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PENETRATION OF PENICILLIN INTO THE EYE

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NEW YORK

The good results of penicillin in treatment of some experimental intraocular infections of the anterior segment of the eye [1] and the antibacterial activity of penicillin in vitro against most organisms found in intraocular infections suggested the study of the penetration of penicillin into the anterior chamber.

The investigations on the topical use of penicillin deal, first, with the entrance of penicillin into the aqueous of rabbits after iontophoresis as compared with that after the corneal bath; second, with the influence of wetting agents on the penetration of penicillin, and, finally, with the possibility of its introduction by repeated use of solutions or ointments with and without wetting agents. The studies on the systemic application are limited to determinations of penicillin in the blood, the spinal fluid and the intraocular fluids after single intramuscular injections.

The penicillin used in these experiments was obtained from a strain of Penicillium notatum grown by Dr. Gladys Hobby. It was extracted as a relatively crude preparation and converted to its sodium salt in the laboratory of Dr. Karl Meyer.[2] Its inhibitory activity ranged at about 1.24 micrograms per cubic centimeter against a 10^{-4} dilution of an eighteen hour broth culture of Diplococcus pneumoniae type III. Although actual titrations by the Oxford method were not made, 1 mg. of the crude preparation was estimated to be equal to 100 to 150 Oxford units.

TECHNIC

The procedures of iontophoresis and the corneal bath were the same as those described in a previous paper [3] except for the applicator tube, which was constricted near its base for the conservation of fluid. In view of the technic best suited for clinical therapy, local anesthesia was preferred to general anesthesia for iontophoresis and the corneal bath. In the latter procedure a 0.25 per cent solution of sodium penicillin was applied for five minutes; in the former solutions of 0.1 and 0.25 per cent were employed at 2 milliamperes for five minutes.

Three wetting agents were studied. They were aerosol 1B (dibutyl sodium sulfosuccinate), aerosol OT [4] (dioctyl sodium sulfosuccinate) and penetrasol B,[5] which consists of aerosol 1B,

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1. von Sallmann, L.: Penicillin and Sulfadiazine in the Treatment of Experimental Intraocular Infection with Pneumococcus, Arch. Ophth. **30**:426 (Oct.) 1943.

2. Meyer, K.; Chaffee, E.; Hobby, G. L.; Dawson, M. H.; Schwenk, E., and Fleischer, G.: On Penicillin, Science **96**:20, 1942.

3. von Sallmann, L.: Sulfadiazine Iontophoresis in Pyocyaneus Infection of Rabbit Cornea, Am. J. Ophth. **25**:1292, 1942.

4. This drug is supplied by the American Cyanamid and Chemical Corporation.

5. Hermann, F.; Sulzberger, M., and Baer, R.: New Penetrating Vehicles and Solvents, Science **96**:451, 1942.

xylene, propylene glycol and antipyrine. A 0.25 per cent solution of sodium penicillin containing aerosol 1B and penetrasol B, each in a concentration of 1 per cent, was applied in the form of a single corneal bath for five minutes. Control experiments consisted of corneal baths with these wetting agents alone. Zephiran chloride, in a dilution of 1:3,000, as used by O'Brien and Swan,[6] had to be discontinued because its antibacterial activity interfered with the determination of the amount of penicillin. Aerosol 1B and penetrasol B, on the other hand, did not exert any bacteriostatic effect in vitro, nor did they diminish noticeably the action of penicillin.

The solutions for repeated instillation contained 0.25 per cent sodium penicillin alone or with the addition of 0.5 per cent aerosol 1B. The same concentration of aerosol 1B was used for the control experiment. Two drops of each solution was instilled at twenty minute intervals over a period of three hours. Twenty minutes after the final instillation aqueous was withdrawn under sterile conditions.

The ointments, prepared by Dr. Karl Meyer, represented two types of emulsion systems. In the first the free acid of penicillin was dissolved in chloroform and mixed with anhydrous wool fat containing 10 per cent liquid petrolatum. The chloroform was then evaporated in vacuo. The same procedure was followed with the addition of a wetting agent, aerosol OT, in a concentration of 1 per cent. The second type of ointment was an oil-in-water emulsion, from which, according to the experiments of Klein and Scheffer[7] and Klein,[8] the resorption of iodides and alkaloids exceeded about twenty times that from the usual water-in-oil emulsions. The penicillin was dissolved in equal parts of propylene glycol and water to a concentration of 20 per cent of the base, lard U. S. P. Aerosol 1B was added to a sample in a concentration of 0.25 per cent. In all cases except the control experiments with a simple aerosol B salve the ointment contained 0.25 per cent penicillin. Syringes were filled with the salve, and 0.1 cc. was applied to each eye at intervals of thirty minutes over a period of three hours. Thirty minutes after the final application the eyes were rinsed well with nupercaine and aqueous was withdrawn under sterile conditions.

In the experiments on systemic introduction a saline solution containing 20 mg. of sodium penicillin per kilogram of body weight was injected into the hip muscle of the rabbits. Blood was withdrawn at intervals of fifteen, thirty, forty-five, sixty and seventy-five minutes after injection; primary aqueous, at intervals of fifteen, thirty and forty-five minutes; secondary aqueous, at intervals of forty-five and sixty minutes, and vitreous and spinal fluid, at intervals of forty-five, sixty and seventy-five minutes.

The quantitative estimation of penicillin in the ocular fluids, in the blood serum and in the spinal fluid was based on their antibacterial activity. Of the four methods described,[9] the dilution method of Fleming appeared best suited for the purpose of these experiments.

After the given intervals the eyes of the rabbits were anesthetized locally with a sterile solution of 0.1 per cent nupercaine hydrochloride. The surface of the cornea at the place of insertion of the needle was touched with a 3 per cent solution of tincture of iodine, and 0.2 cc. of aqueous was withdrawn from each eye and added to two small culture tubes which contained the same amount of neopeptone broth. Blood, vitreous and spinal fluid were obtained with the usual sterile technic, and two series were set up for each sample. Serial dilutions were made, and to each dilution of the parallel series was added 0.2 cc. of an eighteen hour broth culture of D. pneumoniae type III, diluted 10^{-4} in neopeptone broth. For each group of experiments performed on the same day two control series were run with appropriate dilutions of the same solution of sodium penicillin as that used in the rabbits. The cultures were incubated for eighteen to twenty-four hours and examined for inhibition of bacterial growth. From the bacteriostatic activity of the dilution of penicillin in the control series and the inhibitory action of the tested fluids, the concentration of penicillin in the

6. O'Brien, C. S., and Swan, K. C.: Carbaminoylcholine Chloride in the Treatment of Glaucoma Simplex, Arch. Ophth. **27**:253 (Feb.) 1942.

7. Klein, N., and Scheffer, L.: Experimentelle Untersuchungen am Auge über die Resorption aus Salben, Arch. f. Ophth. **128**:460, 1932.

8. Klein, M.: Beitrag zur Resorption aus Augensalben: II. Die Resorption des Atropins, Arch. f. Ophth. **129**:413, 1932; Zur Kenntnis der Resorption aus Augensalben: III. Die Resorption des Homatropins, Pilocarpins, und Eserins, ibid. **131**:25, 1933.

9. Fleming, A.: On the Antibacterial Action of Cultures of a Penicillium with Special Reference to Their Use in the Isolation of B. Influenzae, Brit. J. Exper. Path **10**:226, 1929. Abraham, E. P.; Chain, E.; Fletcher, C. M.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin, Lancet **2**:177, 1941. Fleming, A.: In Vitro Tests of Penicillin Potency, ibid. **1**:732, 1942. Rammelkamp, C. H.: A Method for Determining the Concentration of Penicillin in Body Fluids and Exudates, Proc. Soc. Exper. Biol. & Med. **51**:95, 1942.

latter was calculated in micrograms per cubic centimeter.[10] Repeated controls with plain aqueous humor were made to exclude any antibacterial effect of this fluid.

RESULTS

Local Applications.—The iontophoretic introduction of a 0.25 per cent solution of sodium penicillin into the aqueous led in forty-five minutes to a maximal concentration of 40 micrograms per cubic centimeter (fig. 1). The average for this maximal concentration was about three times as great as that obtained with a solution of 0.1 per cent sodium penicillin and was almost ten times as great as the average concentration in the aqueous forty-five minutes after a single corneal bath with a 0.25 per cent solution. A small amount of penicillin was found in the aqueous after four hours only with the iontophoretic introduction of a 0.25 per cent solution. The increased speed of penetration under the influence of an electric current is demonstrated by the results of determination of penicillin in the aqueous fifteen minutes after application. Whereas no trace of penicillin was detected after a corneal bath, the presence of 16.6 micrograms per cubic centimeter was

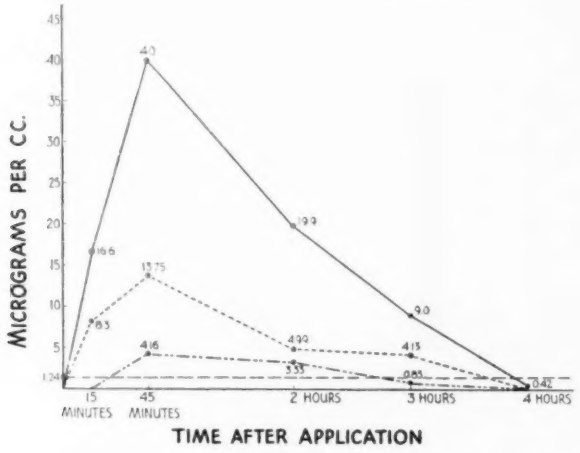

Fig. 1.—Concentration of penicillin in the aqueous humor after application to the cornea. Each figure represents the average of five experiments.

The solid line represents values for iontophoresis with 0.25 per cent solution of sodium penicillin; the line of dots, values for iontophoresis with a 0.1 per cent solution of sodium penicillin; the line of dots and dashes, values for the corneal bath with 0.25 per cent solution of sodium penicillin, and the line of dashes, micrograms of sodium penicillin per cubic centimeter necessary to inhibit growth of D. pneumoniae type III $10.^{-1}$ (The last figure is applicable only to the preparation of the penicillin salt used in the experiments concerned with local introduction.)

estimated after ionization with a 0.25 per cent solution. No detectable amount of penicillin was found in the vitreous which was withdrawn in 2 experiments one hour after the transcorneal iontophoretic introduction of a 0.25 per cent solution of sodium penicillin.

In the first group of experiments with wetting agents nupercaine hydrochloride was employed as the local anesthetic. The addition of aerosol 1B in a concentration of 1 per cent to a 0.25 per cent solution of sodium penicillin applied in the

10. These values are subject to errors inherent in dilution methods. The calculated values for concentration of penicillin in the aqueous do not represent the actual weight of pure penicillin but are relative to the preparations used. It would probably be more accurate to express the concentrations in terms of activity.

form of a corneal bath for five minutes produced in the aqueous an antibacterial activity of 5 micrograms per cubic centimeter, or only slightly more than that obtained with a corneal bath without a wetting agent (fig. 2).

In order that the effect of nupercaine on the permeability of the cornea might be eliminated, general anesthesia with pentobarbital sodium was used in the second group of experiments. The influence of the wetting agent on the penetration of the penicillin solution employed in a corneal bath was more significant under these conditions. The addition of aerosol 1B in a concentration of 1 per cent led to an antibacterial activity of the aqueous which was five times that with a simple corneal bath. The effect of penetrasol B was less pronounced.

Frequent instillations of the 0.25 per cent solution of sodium penicillin with and without the addition of aerosol 1B gave in 2 instances erratic results, but in 4 experiments no inhibitory activity of the aqueous could be detected. In 12 experiments frequent applications of the two types of ointments (page 2) with and without wetting agents did not result in any antibacterial activity of the aqueous. After three hours the irritation of the lids, conjunctiva and cornea, consisting of

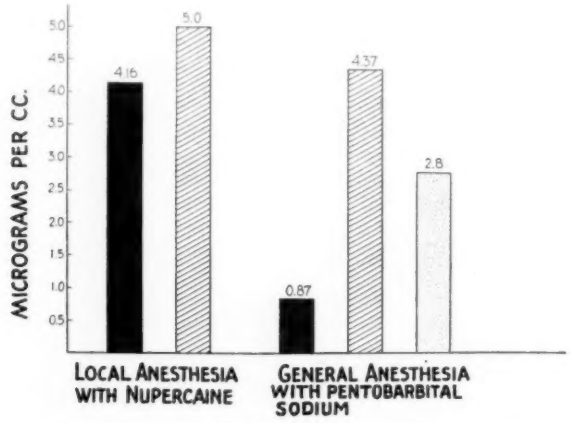

Fig. 2.—Concentration of penicillin in the aqueous humor forty-five minutes after a five minute corneal bath. Each figure represents the average of five experiments.

The black areas represent values for 0.25 per cent sodium penicillin; the cross hatched areas, values for 0.25 per cent sodium penicillin and 1 per cent aerosol 1 B, and the dotted area, values for 0.25 per cent sodium penicillin and 1 per cent penetrasol B.

swelling of the lids, mucopurulent discharge, chemosis of the conjunctiva and haziness of the cornea, was severe with the application of aerosol OT in a concentration of 1 per cent. These signs were moderate or negligible with ointments containing 0.25 per cent aerosol 1B.

The figures on the graph and chart (figs. 1 and 2) represent an average for the results of 5 experiments.

Systemic Introduction.—Of the samples of blood, the first, taken fifteen minutes after the intramuscular injection, showed the greatest antibacterial activity. As figure 3 shows, the amount of penicillin in the blood decreased regularly to about one seventh of its maximum at the end of an hour. The primary aqueous did not inhibit bacterial growth fifteen minutes after injection but demonstrated a moderate antibacterial activity in the samples taken at the thirty and the forty-five minute period. Secondary aqueous, withdrawn forty-five and sixty minutes after injection and thirty minutes after the first paracentesis, inhibited bacterial growth

in considerably higher dilutions than did the primary aqueous. No activity was detected in samples of vitreous and spinal fluid taken at intervals of forty-five, sixty and seventy-five minutes after the injection of penicillin. The figures on the graph (fig. 3) represent an average of the results of 3 to 6 experiments.

COMMENT

Two concentrations of sodium penicillin, 0.1 and 0.25 per cent, were selected for iontophoretic introduction on the basis of previous experiments on intraocular infections and in view of the clinical applicability. With a single application no damage was caused except for transient haziness of the corneal epithelium. With a 0.25 per cent solution the antibacterial activity of the aqueous was evident for almost four hours. The highest concentration, obtained after forty-five minutes, was thirty-two times the amount necessary for in vitro inhibition of a pneumococcus culture in a dilution of $10.^{-1}$ Without use of the electric current the same solution

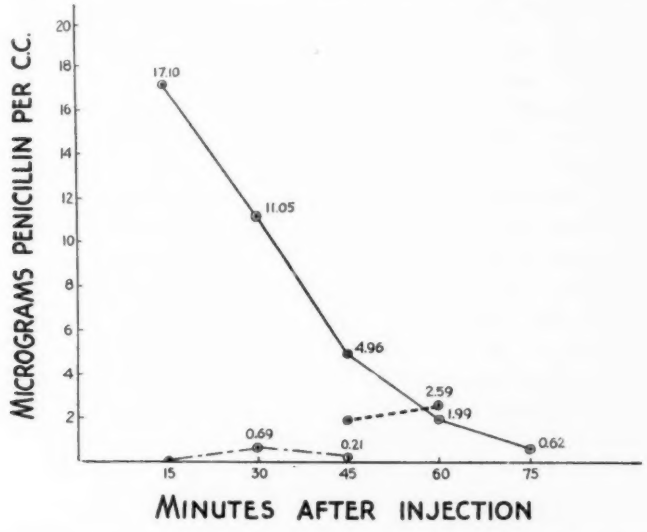

Fig. 3.—Concentration of penicillin in the blood and in the primary and the secondary aqueous of rabbits after a single intramuscular injection of 20 mg. of sodium penicillin per kilogram of body weight. A concentration of 0.415 microgram per cubic centimeter of the sodium penicillin preparation used in this group of experiments was necessary to inhibit growth of D. pneumoniae type III $10.^{-1}$

The solid line represents values for the blood; the line of short and long dashes, values for primary aqueous; and the line of short dashes, values for secondary aqueous.

applied in a corneal bath led to a maximal concentration that was more than three times the amount necessary for inhibition in vitro. Two hours after the corneal bath the aqueous still exhibited an antibacterial activity. These observations explain to a certain extent the surprisingly good results of the corneal bath in the penicillin treatment of experimental pneumococcic infections of the anterior segment of the eye.[1] The therapeutic effect of the corneal bath on such infections was only slightly inferior to that of iontophoresis. As compared with the rapid resorption of penicillin from the blood stream,[11] the rate of depletion from the anterior chamber is moderately slow and is similar to that of sulfadiazine.[3]

11. Rammelkamp, C., and Keefer, C.: The Absorption, Excretion, and Distribution of Penicillin, J. Clin. Investigation **22**:425, 1943.

O'Brien and Swan [6] stated that the penetration of carbaminoylcholine chloride into the aqueous can be greatly increased by dissolving it in a vehicle containing a wetting agent, zephiran chloride. Boyd [12] confirmed this activity of zephiran in experiments with physostigmine. According to Gifford,[13] Bellows achieved experimentally an extreme increase in the penetration of sulfonamide compounds into the aqueous by the addition of various wetting agents. In this study with penicillin the addition of aerosol 1B or of penetrasol B enhanced the introduction of the drug in a single application. Penetrasol B was more irritating and less effective. The maximal concentration of penicillin in the aqueous was, however, about one-eighth that achieved with iontophoresis. Furthermore, a comparison of the two groups of experiments demonstrates that the use of nupercaine as a local anesthetic is almost as effective in increasing the penetration of penicillin into the anterior chamber as is the addition of wetting agents to the penicillin solution in its application with general anesthesia. As these experiments were confined to the use of two surface tension depressants, no generalization can be made as to the value of other wetting agents for use with penicillin.

Penicillin applied in salves did not produce any bacteriostatic activity of the aqueous. Conclusions cannot be drawn, however, as to whether the vehicle inactivated the labile compound or whether no resorption occurred from the vehicle. After repeated instillation of the watery solution usually the presence of penicillin was not detected despite the combination with a wetting agent, but two questionable figures indicate that this type of application may give erratic results. Experiments with ointments and instillations failed in their main purpose of providing a means of retention over a longer period of a moderate concentration of penicillin in the aqueous after the steep, but transient, rise following iontophoresis.

The studies were not extended to the estimation of the amount of penicillin in the cornea and lens because the usual extraction methods could not be applied to the labile penicillin without a further increase in the margin of error. Negative results were obtained in 2 experiments with vitreous fluids, withdrawn after the iontophoretic introduction of penicillin.

Rammelkamp and Keefer [11] reported that the spinal fluid of human subjects given intravenous, subcutaneous and intramuscular injections of penicillin did not exhibit any antibacterial activity. The same results were obtained in the experiments reported here with the intramuscular injection in rabbits. The aqueous, however, demonstrated a moderate but definite inhibitory action thirty to forty-five minutes after the injection. The secondary aqueous contained considerably more penicillin than the primary aqueous.

It can be concluded that systemic treatment with penicillin will be beneficial for ocular infections. It is possible that the efficacy of local penicillin therapy, as shown by previous experiments, can be further increased by the combination of topical application and systemic introduction.

SUMMARY

1. The antibacterial activity of the aqueous in vitro served as the basis for determination of the amount of penicillin in the anterior chamber of rabbits after various methods of local application of the sodium salt.

12. Boyd, J. L.: Quantitative Comparison of Methods of Administering Physostigmine, Arch. Ophth. **30**:521 (Oct.) 1943.

13. Gifford, S.: Personal communication to the author.

2. Comparison of the penetration of penicillin into the aqueous after the iontophoretic introduction with that following the corneal bath with and without wetting agents showed that the ionization method increases the concentration of penicillin in the aqueous ten times as much as the corneal bath and about eight times as much as the corneal bath with the addition of a wetting agent, aerosol 1B.

3. After a single iontophoretic application of a solution of the sodium salt of penicillin, the aqueous exhibited an antibacterial activity for almost four hours; after a single corneal bath with a solution of the same concentration, the antibacterial activity continued little more than two hours.

4. Repeated applications of solutions and ointments containing penicillin did not produce any detectable antibacterial activity of the aqueous. The addition of wetting agents was without effect.

5. Small amounts of penicillin entered the aqueous from the blood stream. Secondary aqueous contained several times as much penicillin as primary aqueous.

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PATHOLOGIC CHANGES IN THE LENS ASSOCIATED WITH NONTRAUMATIC IRITIS

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In a previous paper [1] I described structural changes in a lens during the active stage of a corneal ulcer as they are seen microscopically, and in a second paper,[2] the changes that may result long after an ulcer has been replaced by scar tissue. The present paper, the third in the series, has for its object a microscopic study of lesions occurring in a lens in nontraumatic iritis.

Ordinarily, a lens remains clear after a first attack of iritis; it is only after repeated attacks that opacities in the lens appear. I recall but 1 case, that of an able-bodied man of 54, in which cataract developed during a first attack of iritis. The iritis lasted about two months and was marked by an enormous infiltration in the stroma and a lenticular mass of exudate in the anterior chamber. The pain was of a rheumatic, intractable character. For a short period the tension was elevated, paracentesis being required to relieve it. After several weeks a sector-shaped area of necrosis appeared in the iris. At the end of the attack opacities appeared in a sector-shaped area of the cortex of the lens. Vision, which had been normal, was reduced to 20/40 and remained so.

Clinically, this case was interesting not alone because of the development of a cataract during a single attack of iritis but because the cataract did not lie under the necrotic sector of the iris. The eye was observed for years after the iritis had subsided. The tension was always normal, and the cataract was stationary.

PATHOLOGIC MATERIAL

In this study, microscopic examination was made of the lenses in 20 globes with nontraumatic iritis. A majority of the globes had been enucleated because of tuberculosis of the uvea, usually of the conglomerate type. In 2 globes Cysticercus was discovered; 1 had been involved in sympathetic ophthalmia, and in 1 a retinoblastoma was present; in 1 globe the condition was mistakenly diagnosed as retinoblastoma, and 2 specimens showed syphilitic iritis.

GENERAL CONSIDERATIONS

Pathologically the symptoms of iritis are commonly classified under two main heads, namely, hyperemia and exudation into the stroma of the iris and into the chambers of the eye. In many physical ways, usually obvious in life, an exudate into the chambers may involve the lens. In mild iritis the pupillary border may become adherent to the capsule of the lens without a demonstrable membrane. In severe iritis, with exudation into the posterior chamber, the entire posterior surface of the iris may be plastered to the capsule of the lens and to the ciliary processes. The pupillary area of the lens may be covered by an exudate—occlusion of the pupil—which may occur independently of an adhesion of the pupil to the lens—seclusion of the pupil. It is known anatomically that every instance of

Read before the American Ophthalmological Society, Hot Springs, Va., June 12, 1943.

1. Samuels, B.: Tr. Am. Ophth. Soc. **39**:66, 1941.
2. Samuels, B.: Tr. Am. Ophth. Soc. **40**:292, 1942.

severe iritis is to some extent accompanied by cyclitis. Hence the word iritis has come to connote iridocyclitis. Owing to the cyclitis, the posterior capsule of the lens may be covered by exudate, which reaches it by way of the vitreous. It is possible for the entire lens to be engulfed in an exudate or to be held in a cyclitic membrane.

In cases of iridocyclitis the position of the lens may be changed so that its capsule and the zonular fibers are put on the stretch, as when an aqueous which is too albuminous or too cellular blocks the spaces of the pectinate ligament and accumulates in the chamber. In this way the depth of the chamber may be increased and the lens pressed backward and compressed against the vitreous. The reverse may happen when a contracting cyclitic membrane throws the lens forward, compressing it against the cornea and the iris. It is known that traction and pressure on the lens, especially when the latter is directed against the resistant cornea, dispose to the formation of the cataract.

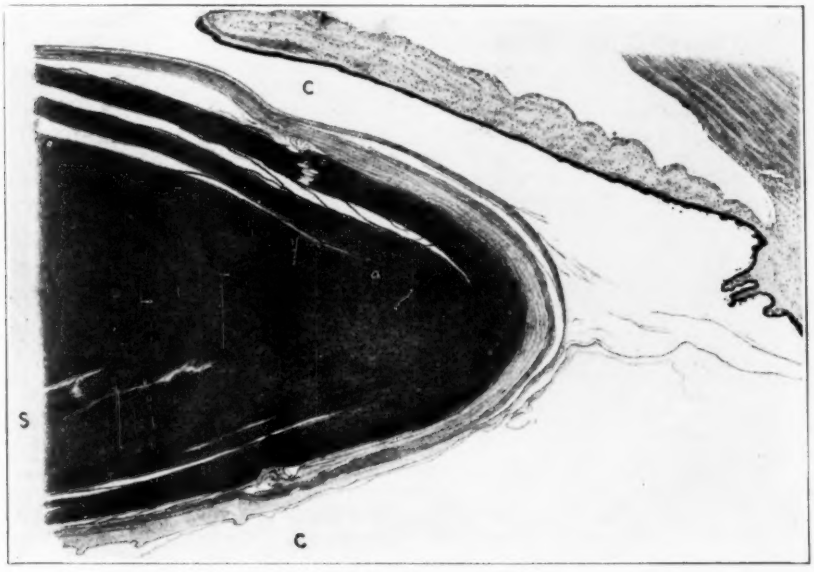

Fig. 1.—Heterochromia, iritis and cataract. The iris is poor in pigment. The angle of filtration is open. The subcapsular layers of the lens are differentiated from the nucleus by their lighter stain and irregularity. At the lower *C* there is a spot of broken-down cortical layer. Similar spots of decay are seen at *S* and the upper *C*. The germinal zone is reduced to a small area, which is considered to be a sign of cataract.

STUDY OF THE MATERIAL

Lesions in the lens, because of the absence of blood vessels in the organ, are regularly referred to as degenerative. The subject is often dismissed with little beyond this statement. Nevertheless, owing to the visibility of the lens in life and its surgical importance, the most minute change within its substance assumes peculiar interest and importance.

REPORT OF SPECIAL CASES

CASE 1.—*Heterochromic cataract* (from a cadaver).

The history stated that the lens had a peculiar bluish gray marking, which had changed little over a long period. In the specimen (fig. 1) there was a narrow stratum of irregular and partially destroyed cortical fibers which extended around the entire circumference of the

lens. In life this zone could not have been quite clear, but was probably translucent—hence the peculiar color. Another remarkable feature was the almost perfect preservation of the subcapsular epithelium in the presence of adjacent diseased lens fibers, a condition indicating that the metabolism of the lens was never much disturbed and accounting for the stationary character of the cataract.

CASES 2 AND 3.—*Intraocular cysticercosis.*

The 2 globes containing a cysticercus presented signs of greater toxicity than the eyes with tuberculosis. In 1 case a cysticercus was present in the anterior chamber of the eye. Suddenly, fourteen days before enucleation, a large staphyloma intercalare developed, under which the parasite was visible microscopically. Adjacent to the staphyloma an unusual event had taken place, namely, spontaneous rupture of the capsule of the lens.

In the other case a cysticercus in the vitreous had set up a violent iridocyclitis, causing formation of membranes in the vitreous and detachment of the retina. The interesting features were the disappearance of the posterior capsule of the lens, the invasion of the lens by pus cells and the absence of the entire epithelial system of the lens, resulting in a rare lesion—a "dead lens."

CASE 4.—*Sympathetic ophthalmia.*

For eighteen months before enucleation iritis had been present. Because of increased tension, an iridectomy was performed. Shortly after the operation a violent inflammation broke out in the fellow eye, which soon became blind. It could not be proved that this case was one of true sympathetic ophthalmia because spontaneous iritis and secondary glaucoma had ante-

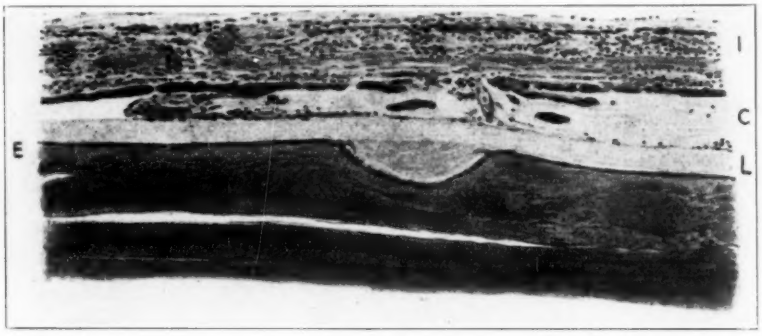

Fig. 2.—An eye removed because of tuberculosis of the retina and secondary glaucoma. The lens is cataractous. A thick layer of hyalinized connective tissue (*C*) binds the iris (*I*) to the capsule of the lens (*L*). The latter is lined by a single layer of epithelial cells (*E*), which at one spot detaches itself from the capsule and dips down into the lens. The space so formed is filled with a homogeneous substance, supposed to be a druse of the capsule.

dated the operation. It may have been a case of bilateral malignant endogenous iritis leading to blindness under the guise of a clinical diagnosis of sympathetic ophthalmia. In such a case the anatomic changes characteristic of sympathetic ophthalmia are present.

Microscopically (fig. 5) the iris was transformed into a tumor-shaped mass, which clinically could have been mistaken for iris bombée. A very cellular subcapsular cataract not only covered the pupillary area but extended beyond the equator on both sides. It demonstrated that a widespread capsular cataract may form in a period of eighteen months.

CASE 5.—*Retinoblastoma.*

In this case the pathologic picture did not correspond to the clinical description. The lens had been recorded as opaque, with a chalky white appearance. The lesion proved to be a dense subcapsular cataract, 4 mm. in diameter (fig. 4). If one had undertaken the removal of the lens, one would have been prepared to encounter a hard structure, and not a soft one, lying under a subcapsular cataract. The tumor of the retina lay in contact with the lens. The question arose whether the tumor or the iritis had produced the cataract. It was decided that poisonous substances from the tumor first produced the iritis, as sometimes happens in cases of retinoblastoma, and that this, in turn, produced the cataract, after occlusion and seclusion of the pupil.

CASE 6.—*Condition mistakenly diagnosed as retinoblastoma.*

The eye of a boy 6 years of age became blind from secondary glaucoma four weeks before it was enucleated. This case belonged to a small group of cases of iridocyclitis in which, in spite of shrinking membranes and detachment of the retina, glaucoma supervenes and the eye stays hard. It is the fate of most eyes with this condition to be enucleated under a mistaken diagnosis of retinoblastoma. The lens was described as clear. Microscopically (fig. 6), a focus of spindle-shaped cells lay on the internal surface of the capsule posteriorly, in the part of the capsule that bounds the recessus hyaloideocapsularis. In the recessus itself, exactly opposite the focus mentioned, there lay another focus, this one being composed of lymphocytes, epithelioid cells and giant cells. The observations pointed to the following conclusions:

1. A focus of exudation on the external surface of the lens may irritate the overlying epithelial cells so that they produce a focus of cells similar to connective tissue cells.

2. It is possible for the epithelial cells that have proliferated as far back as the ligamentum hyaloideocapsularis to produce spindle-shaped cells, a feat commonly ascribed to the anterior subcapsular cells.

3. The anterior subcapsular and the equatorial cells probably have more in common than is indicated by Salzmann's theory of their being biologically widely different. It is certain that in this instance the posterior, abnormally placed, cells, under the stimulus of an exudate

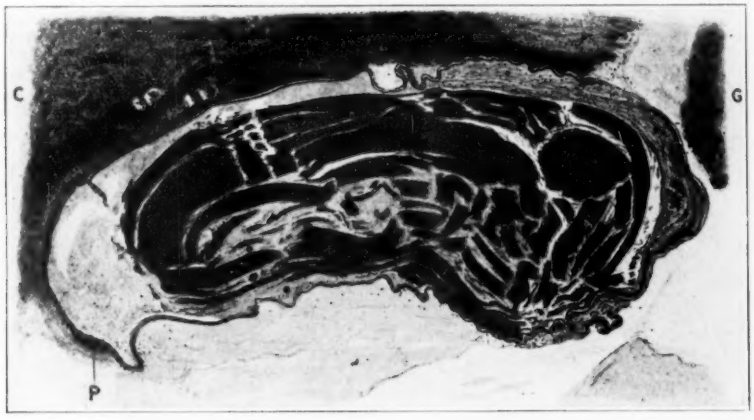

Fig. 3.—In a girl 10 years of age, the entire iris and ciliary body have been replaced by the granulation tissue of tuberculosis (*G*). The lens is shrunken. An eccentric subcapsular cataract extends from the middle of the anterior surface to beyond the equator. The cortical layers throughout and much of the nucleus are liquefied. To the left the capsule is covered with pus cells (*P*), and there the epithelium of the lens is entirely missing.

on the surface, behaved much as the anterior, normally placed, cells would have been expected to do under a similar irritation.

4. Possibly the reason that the anterior subcapsular cells commonly produce a connective tissue-like substance (the subcapsular cataract) and that the equatorial cells seldom do lies not so much in the biologic difference between the two groups of cells as in a dissimilarity of the exciting agents. A noxious substance from an inflamed ciliary body that acts on the equatorial region of the lens is not considered as destructive as one from the cornea that acts on the pupillary region. It is interesting to note that from inflammatory lesions in the body a substance called leukotaxine, responsible for the local migration of leukocytes, as in hypopyon keratitis, has been isolated in pure crystalline form.

CASE 7.—*Druse of the capsule of the lens* (fig. 2).

An abrupt thickening of the capsule was considered to be a druse laid down by the epithelial cells as an expression of malnutrition resulting from an overlying hyalinized membrane. This specimen was reminiscent of the eye with heterochromic cataract in that, while there had been extensive destruction of the cortical layers, the epithelial system showed little alteration in general.

CASE 8.—*Detachment of the germinal zone of the lens.*

A man aged 60 had had a syphilitic infection five months before. Two months later violent iritis broke out, with the formation of a cataract and a pupillary membrane, followed shortly by blindness. Microscopically (fig. 7) there was an unusual combination of an anterior capsular cataract and detachment of the germinal zone of the lens, the latter being due to extensive liquefaction of the cortex. The retina showed enormous infiltration of the internal layers and great thickening of the walls of the precapillaries. As such a rapid and widespread destruction of the lens is not seen in cases of the most severe iritis, probably an error was not made in ascribing the liquefaction to retinitis rather than to iritis.

SUMMARY OF GENERAL PATHOLOGIC CHANGES

Glaucoma.—In 6 cases the existence of glaucoma was mentioned in the history, but in a number of other cases there must have been periods of increased tension, especially in several in which iris bombée was present. Increased tension of itself leads to cataract.

Degree of Iritis.—In every instance, with the exception of the case of heterochromic cataract, extensive adhesions gave evidence that the iritis had been severe.

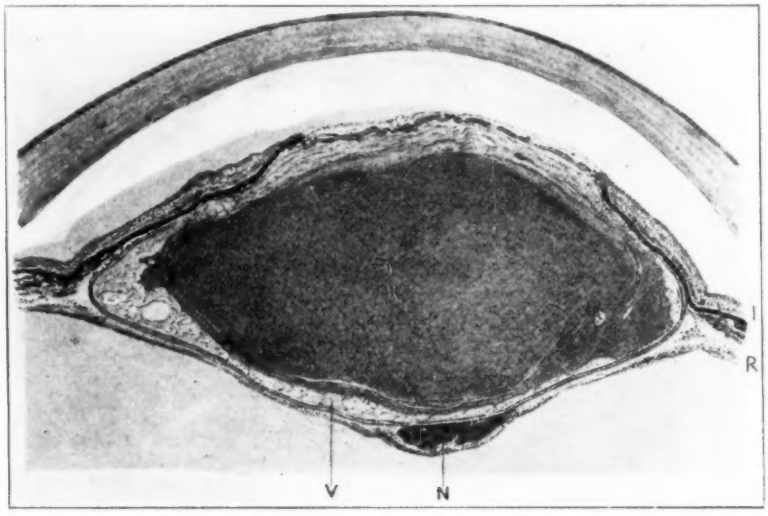

Fig. 4.—A retinoblastoma had led to severe iritis. The retina (*R*) is pressed against the lens, and a nodule of the tumor is shown at *N*. The iris (*I*) is adherent to the lens, the pupillary area of which is covered by a membrane. There is an extensive subcapsular cataract. The concentric particles around the nucleus are fine granules of chalk in the early stage of calcification. The equatorial and posterior capsules are lined by a single row of epithelium, and this, in turn, is covered with vesicular cells (*V*).

Generally, at the posterior pole there was little in the vitreous in the way of exudate or membranes that could have affected the lens physically.

Rupture and Destruction of the Capsule of the Lens.—Rupture of the capsule of the lens in 1 of the cases of cysticercosis and its partial destruction in the other have been mentioned. There was a second case of partial destruction of the capsule, in which the iris had been replaced by a conglomeration of tubercles that filled the anterior chamber. The disappearance of the adjacent portion of the lens capsule was an expression of the malignant property of tuberculosis to erode whatever it touches. Since in all 3 cases the iritis had been exceptionally severe, the conclusion was reached that spontaneous destruction or rupture of the capsule of the lens is an event seldom to be feared in cases of ordinary iridocyclitis. The capsule is brittle but tough.

Folds in the Capsule of the Lens.—In 14 cases the capsule showed folds of various sizes. Ruffling and folds of the capsule are typical of cataract.

Changes in the Epithelium.—In this series of cases of spontaneous iritis the epithelium behaved in ways similar to those observed in the cases of corneal scar. There were 8 cases of extensive subcapsular cataract, in several of which it straddled the equator.

Death of the Subcapsular Epithelium.—In the entire series there was only 1 instance, a case of cysticercosis, in which the entire epithelium had disappeared so that the lens was really "dead." In view of the great amount of destruction of the substance of the lens in some of the cases, it is remarkable that the epithelium should have been spared.

Changes in the Substance of the Lens.—In general, the changes in the substance of the lens in this series differed little from those in the 36 lenses described in the paper on corneal scar.[2] As a special feature in this series, subcapsular vacuoles were present in most of the lenses. In 1 lens the vacuoles were confined to the posterior cortical layers and were in contact with the capsule. In this lens the substance should have shelled out easily in an extracapsular extraction. Some

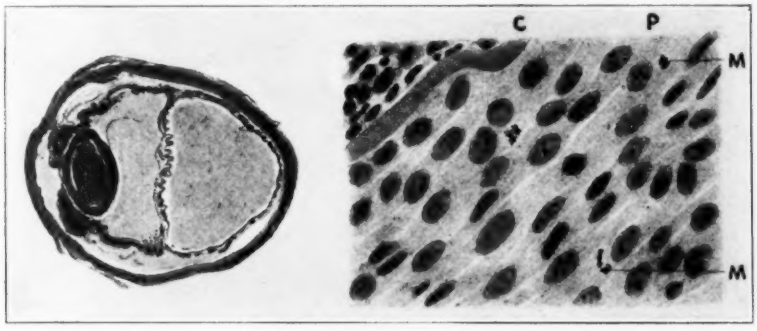

Fig. 5.—Sections in a case of sympathetic ophthalmia. At the left is shown the tumor-like infiltration of the iris, which clinically simulated iris bombée. A nodular infiltration is seen in the ciliary body and in the choroid. In the detail to the right, the capsule of the lens (*C*) is covered with lymphocytes and epithelioid cells from the iris. The mass of cells on the posterior surface of the capsule (*P*) represents rapid proliferation of the capsular epithelium. A few mitotic figures (*M*) are visible, an unusual observation. The cells of the cataract bear a striking resemblance to those of the infiltration in the iris.

lenses showed extensive liquefaction and calcification of their substance. In 2 lenses the liquefaction went so far as to produce a genuine morgagnian cataract. Occasionally a lens was decidedly swollen.

Vesicular Cells.—Vesicular cells were noted less often in the present series than in cases of corneal scar, although in 4 lenses they were numerous. It is worthy of note that in 2 lenses vesicular cells were located beneath the anterior capsule, at a distance from their usual site at the equator. In 1 lens the germinal zone was replaced by a large group of vesicular cells. In another lens a great cavity was seen in the germinal zone which was probably produced by the bursting of vesicular cells and their confluence.

SPECIAL TYPES OF PROLIFERATION OF THE EPITHELIUM OF THE LENS

Flat Proliferation.—Several times after the disappearance of the germinal whorl, the capsule at the equator was left completely bare of epithelium. More often

a single row of epithelial cells remained in immediate contact with the capsule and proliferated backward until it lined the entire posterior capsule. This is an occurrence especially characteristic of cataract following detachment of the retina. At the posterior pole, as a rarity, vesicular cells were interposed between the row of epithelial cells and the nucleus of the lens. The impression was gained that the presence of one type of cells excludes the presence of the other. It seemed that when the medium was not favorable for the formation of vesicular cells, the cells restricted their proliferating power to growing backward along the surface of the capsule. It was noted that the lenses in which the epithelium had lined the capsule throughout were the lenses that showed the greatest amount of liquefaction of the substance. Conversely, a group of vesicular cells was associated with lenses having better preserved substance.

Massive Proliferation.—This type was represented by the fully developed anterior subcapsular cataract. When the anterior subcapsular cataracts in this series and those in the series of cases of corneal ulcer and corneal scar were considered together, enough diversity was noted to suggest the following subtypes:

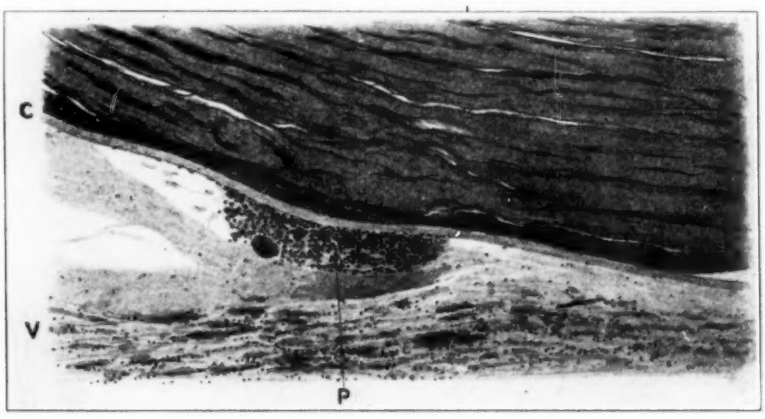

Fig. 6.—The eye of a 6 year old boy who had been blind for four weeks due to the presence of a lesion mistakenly diagnosed as retinoblastoma. In the recessus hyaloideocapsularis, lying between the capsule of the lens (*C*) and the vitreous (*V*), there is a precipitate (*P*) containing a large giant cell. Overlying this the capsule of the lens shows proliferation of spindle-shaped cells. To the left, toward the equator, the epithelium is normal, but to the right, toward the posterior pole, the epithelium is flat and scanty.

1. Widespread Type (figs. 3 and 4) with an Undulating Anterior Surface: In 1 case a cataract of this type attained a diameter of 6 mm., and in rare instances the lesion straddled the equator. The cataract consisted of spindle-shaped cells which had laid down a homogeneous, tough substance. It was frequently lined on its posterior surface by a layer of epithelium continuous with that lining the capsule.

2. Circumscribed Pyramidal Type, Projecting Abruptly Forward in a Cone: Frequently the cataract was located in the exact center of the pupil. Its substance was cellular. It was not easy to understand why the proliferation in this type was so circumscribed and often entirely isolated from the pupillary border of the iris. The production of a pyramidal cataract is commonly ascribed to irritation from the cornea, such as that due to a serpiginous ulcer. However, a pyramidal cataract is not infrequently encountered in cases of detachment of the retina after

inflammation has set in, proof that it may also be caused by an irritating substance coming from the posterior zone of the eye.

3. Type Characterized by Numerous Sharp Wrinkles and Folds of the Anterior Capsule: The stroma consisted of a thin, loose filamentary proliferation of the epithelium.

SIMILARITY OF SUBCAPSULAR CATARACT AND CALLUS *(SCHWIELE)* OF THE CILIARY BODY

The interior of the lens is not the only place in the eye in which the epithelial cells may lay down a substance similar to that of an anterior capsular cataract.

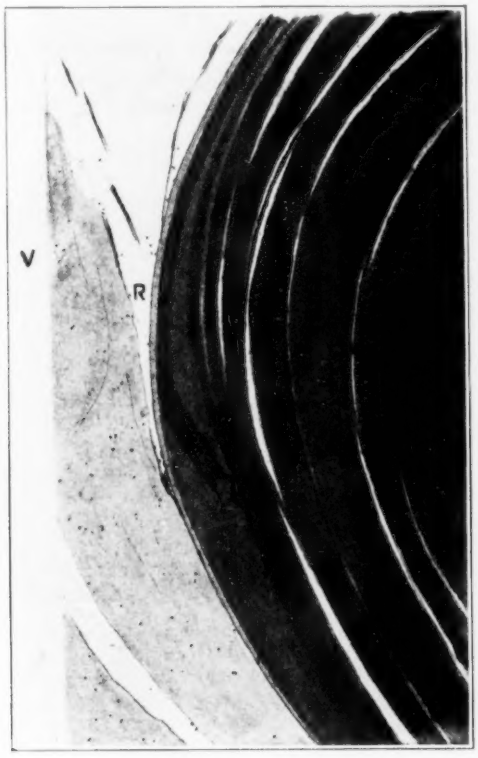

Fig. 7.—Syphilitic iritis in the eye of a man aged 60, who had been blind for three months. A subcapsular cataract (not shown) developed in the pupillary area. At the equator the germinal zone is detached from the capsule. The vitreous (*V*) is pushed forward by the detached retina, and therefore the recessus hyaloideocapsularis (*R*), which as a rule is directed frontally, is here directed anteriorly. The space contains a few red blood cells.

Occasionally, in the study of subcapsular cataracts a similar massive formation lying on the flat part of the ciliary body or on the choroid is encountered. In the latter location the pigmented epithelium may join the nonpigmented epithelium in its formation. A comparison of these connective tissue–like formations of epithelial origin in the various locations never fails to be of interest.

THEORIES OF THE CAUSES OF SUBCAPSULAR CATARACT

In general, the cataracts described in the series of corneal scars were larger than those associated with corneal ulcers. There was no doubt that the smaller

cataracts which developed during the active stage of an ulcer represented the direct response to irritation produced by bacterial action. For the development of the larger cataracts found in the series of cases of corneal scar there must have been some other factor. At the moment of perforation of an ulcer the products of the bacteria are washed out with the aqueous and no longer can accumulate during the fistulating and healing processes. Freedom from bacterial poisons after perforation of an ulcer accounts for the rapidity with which the inflammation in such an eye disappears. I came to the conclusion that faulty metabolism is a factor in the production of the large cataracts seen in eyes with old atheromatous scars of the cornea. The accompanying pigmentary degeneration of the retina in such eyes speaks in favor of a disturbed metabolism throughout the eye.

With respect to the previously mentioned clinical case of a cataract which developed at the end of a single attack of iritis, it was my opinion that the cataract was the result of faulty metabolism in the lens. If the substance leukotaxine from the inflammatory lesion in the iris had been the cause, the cataract should

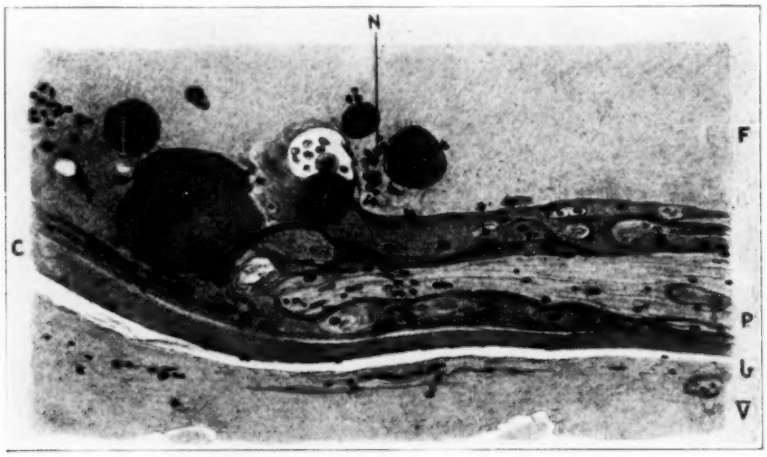

Fig. 8.—A complicated cataract in a case of tuberculosis of the iris. Toward the right, at *P*, is a layer of vesicular cells. At *N* is a group of nuclei, which represent cells originating outside the lens. Most of the nucleus (*F*) is fluid. The vitreous (*V*) shows some cells and fibroblasts. *C* is the capsule of the lens, and *b*, a blood vessel.

have developed during the acme of the attack. The faulty metabolism was attributed to damage suffered by the ciliary body during the prolonged attack of iritis. However, the damage could not have been great because the tension of the eye returned to normal and the cataract did not increase.

The fact that the epithelium and the substance of the lens may both be destroyed by a substance derived from an inflammatory lesion is not to be minimized. This occurs rapidly in association with necrosis of a sarcoma of the uvea and metastatic ophthalmitis. However, because of its inert quality, the lens seems to be able to withstand the mild production of leukotaxine in each attack of recurrent iritis and does not become cataractous until the ciliary body is no longer able to nourish it properly. Analogously, in a case of acute fulminating glaucoma that subsides spontaneously, the ciliary body undergoes changes, although unseen clinically, which are similar to the atrophy and necrosis obvious in the iris. Hence it is that after the attack, in spite of the permanent blockage of the angle of the chamber, the eye may become soft and remain so, the ciliary body being unable

to secrete the normal quantity of aqueous. Nevertheless, the lens takes on a characteristic greenish color and in the end, because of malnutrition, becomes cataractous.

PROLIFERATION OF EPITHELIUM AS AN ATTEMPT AT RESTORATION OF THE ORGAN

In many specimens it was noted that the disintegration of the lens fibers seemed to have antedated the proliferation of the epithelial cells. The massive type of proliferation in shape often resembled a biconvex lens. If the substance of the new formation had been of such nature and regularity as to have assured transparency in the living eye, there would have been no doubt that it represented a true lens superimposed on the original nucleus.

An anterior lenticonus in shape also suggests a small lens superimposed on a larger one. It would be interesting to know whether an anterior lenticonus is a symbol of an irregular and luxuriant activity of the subcapsular epithelium during embryonic life.

NUTRITION OF THE LENS

Throughout the entire study it seemed to be more than a mere coincidence that the epithelial system of a lens confines itself normally to that portion of the capsule bathed in aqueous. That the aqueous can nourish epithelial cells is proved by pathologic observations. Epithelial cells extruded from a rent in the capsule may live free in the anterior chamber indefinitely. Likewise, cells of connective tissue origin may live free in the aqueous. As an example, in cases of sarcoma of the ciliary body detached cells, well nourished, may be seen clinging to and creeping along the zonular fibers.

In the present preparations the epithelial cells that lined the capsule at the posterior pole, notwithstanding that they were anatomically identical with those at the anterior pole, never produced a posterior subcapsular cataract in the sense of an anterior subcapsular cataract. One can speculate that the cells in their new position had not within themselves the power to multiply or that the vitreous did not afford them the required nourishment or that there was no incentive to proliferate.

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THE SOCKET AFTER ENUCLEATION AND THE ARTIFICIAL EYE

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NEW ORLEANS

HISTORICAL REVIEW

Simple enucleation is not the most ancient surgical means of ridding the orbit of the eye. On the contrary, other surgical procedures were adopted until one hundred years ago. In the earlier period an operation that peeled the eye from its capsule was considered brutal as compared with procedures in which the eye was cut open rapidly and the contents eviscerated. To accomplish the latter, it was not unusual to cut away the cornea.

Recall what was designated in an earlier period (1583) as an extirpation—today justifiably denominated the butchery of George Bartisch.[1] He transfixed the eye, having passed through it a large curved needle threaded with tape, and then, pulling on the tape, cut the eye away.

Though Cleoburey [2] introduced the classic enucleation of the eye in 1826, his procedure was not adopted until 1855. Its performance was naturally slow, requiring dexterity and skill. Anesthetics had not yet been discovered. Ferrall [3] and Bonnet [4] have for years been given credit for having originated the procedure of enucleation. However, it is now admitted that the operation was not instituted by them. Cleoburey [2] described the enucleation operation as follows:

OF THE REMOVAL OF THE GLOBE OF THE EYE

The conjunctiva should first be divided with a thin sharp-pointed knife, and next all the muscles inserted into the globe: this being done, the point of the knife would be carried cautiously backwards to the posterior part of the orbit, and the optic nerve divided: the nerve will be more easily divided by directing the knife backwards into the orbit on the nasal side of the globe, as the optic foramen is situated nearer on this side from the centre of the orbit. The operator should be careful not to injure the thin orbitar plate of the frontal bone, otherwise the brain may be injured, and in dividing the nerve, he should avoid stretching it. Very little hemorrhage succeeds this operation, unless the vessels are diseased, when it may be restrained by pressure; the dressings should be as simple as possible.[5]

Ferrall introduced the description of his procedure with the following prefatory comment, and I shall fashion my contribution about these truths.

If it be true, that the clinical studies are most productive which are based upon correct anatomical knowledge, it must also be admitted, that the researches in anatomy are most

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It is in keeping with the spirit of the day that relentless search be made to improve all works of man.

1. Bartisch, G.: Augendienst, Dresden, M. Stöckel, 1583.

2. Cleoburey, W.: A Review of Different Operations Performed on the Eyes, London, T. & G. Underwood, 1826.

3. Ferrall, J. M.: Dublin J. M. Sc. **19**:329, 1841.

4. Bonnet, A.: Ann. d'ocul. **5**:1841.

5. If this statement is true, why should gauze be jammed into the socket after the enucleation; why is the figure-eight bandage tightly applied, and why is hot water used to control "very little hemorrhage"?

profitable to which we are forced to return, by phenomena in disease, unexplained by, or irreconcileable [sic] with the current notions of the structures engaged. It would be an easy and not unpleasing task, to maintain this proposition by a reference to the medical literature of almost every country in civilized Europe.[5]

It must be remembered that it was Jacques René Tenon, French anatomist and oculist, 1724-1816, who discovered the fascia bulbi, from which the eye is peeled, whereupon the cue which set one's wits to work was provided.

However, it is well recognized that even Tenon cannot be given priority for discovery of the fascia bulbi, for Galen, Columbo, Casserinus, Riolon and others had already described this tunic. It was Tenon, however, who described it fully; yet Whitnall [6] stated, in April 1921: "It is the subject of reinvestigation and labored description," and Dwight added: "The complications of this membrane are limited only by the perverted ingenuity of those who describe it."

DEFINITION AND DESCRIPTION

The simple enucleation is here defined as the peeling of the eye from Tenon's capsule. Random severance of muscles and tissues to rid the orbit of the globe is not enucleation but extirpation—however, not the butchery of Bartisch. Though the eyeball is removed entirely by extirpation, enucleation demands that it be shelled out as one does the kernel of a nut. The simple enucleation removes 6.5 volume measurements of the orbit's contents.

When the eye is shelled from the capsule, the muscles are cut from the sclera, but not from the capsule. The belief that the rectus muscles when cut at their attachment to the eye retract extensively is erroneous. Duke-Elder [7] stated:

The muscles are covered by fascial sheaths continuous with Tenon's capsule. At the point where the two fuse, the connection between the muscle fibres and the sheath is especially strong, so that after enucleation of the globe, the muscles retain their attachment to the capsule, and do not retract extensively.

But if, during enucleation, the muscles are cut through the muscle tissues, not the tendon, and outside the capsule, distal to the fascial sheaths, there is a noticeable retraction of the muscles and tissues backward into the orbit, and if the check ligaments are also cut, increased disfigurement of the socket is produced.

Many surgeons assume that a concave cavity is left in the socket after the globe has been removed. Grimsdale and Brewerton [8] stated:

The fat and muscles remaining after the removal of the eye fall together in the orbit and form a concave stump, against which the artificial eye is placed.

This is true regarding improper enucleation but erroneous regarding proper enucleation. In addition, the same authors stated:

The prothesis is concave, and between it and the concave stump a large space is left, in which the secretions accumulate, and, decomposing, irritate the conjunctiva.

The assumed cavity was so definite in the mind of Müller,[9] an artificial eye artisan, that he developed a double shell eye made of glass and on the under belly supplemented a ball to fit the supposed hollow.

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6. Whitnall, S. E.: The Anatomy of the Human Orbit, London, H. Frowde, Hodder & Stoughton, 1921, p. 288.

7. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 1, p. 179.

8. Grimsdale, H. B., and Brewerton, E.: Textbook of Ophthalmic Operations, ed. 2, New York, William Wood & Company, 1920, p. 186.

9. Müller, J.: United States Government patent, 1899.

So, based on certainty that a concavity was left after enucleation, a popular surgical procedure of today provides that a ball be implanted into the capsule of Tenon.[10] The rationale of such a procedure is not clear, for the socket left after such an operation is much the same as that which follows the enucleation. One need but open the lids of patients subjected to enucleation and of those operated on by implantation of a ball into Tenon's capsule to realize that surmises governed instead of facts (fig. 1).

The following declaration is not so readily proved: viz., that after the enucleation of the eye, the tissues come forward in the orbit. Translatory movements of the eye and translatory movement of the socket's tissues after the eye has been peeled out are matters of some importance in clinical ophthalmology and in ophthalmic surgery, for if shown to exist they help to establish the enucleation procedure as having even greater merit than was originally assumed.

Duke-Elder made the following statement (page 581)[7]:

The movements of pure translation (forwards and backwards and from side to side) which are normally permitted to the eyeball are small. If the palpebral aperture is forcibly widened the relief of pressure allows the cornea to move slightly forwards (1 mm., J. Müller [11] 1868; 0.8 mm., Tuyl,[12] 1901) as well as downwards and inwards (Berlin,[13] 1871) and a converse backward displacement accompanies contraction of the lids. These movements are passive and depend on the slight extent to which the orbital fat may be moved and on the pull of the levator palpebrae upon the septum orbitals (Ludwig,[14] 1904; Peschel.[15] 1904; Birch-Hirschfeld,[16] 1912).

Fig. 1.—Characteristic photograph of the socket after enucleation. The depth is seen as a plane tilted backward at the outer upper angle; a ball implanted into Tenon's capsule gives the same picture. A semisphere, with the same dimensions as those of the human eye, and held fast to this plane, may move to a remarkable extent.

It is the pull of the rectus muscles on the globe which compresses the fat of the orbit, and the fatty tissue, although relatively incompressible, is altered in position and shape so that it comes forward in the orbit when unrestrained. It is not simply an engorgement of tissues, which immediately fall into the gap left after enucleation

10. Lang, W.: Tr. Ophth. Soc. U. Kingdom **7**:286, 1887.
11. Müller, J.: Arch. f. Ophth. (pt. 3) **14**:183, 1868.
12. Tuyl, G.: Arch. f. Ophth. **52**:233, 1901.
13. Berlin, T.: Arch. f. Ophth. (pt. 2) **17**:193, 1871.
14. Ludwig, P.: Klin. Monatsbl. f. Augenh. **41**:389, 1904.
15. Peschel, M.: Centralbl. f. prakt. Augenh. **28**:11, 1904.
16. Birch-Hirschfeld, in Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, Berlin, Julius Springer, 1912, vol. 9, pt. 2.

or the fat is unleashed, but the action of the oblique muscles, the check ligaments and the elastic qualities inherent in Tenon's capsule which are concerned.

The oblique muscles participate actively in the forward pull of the tissues, particularly noticeable after enucleation, which leaves revealed a ridge in the socket in evidence of the function of the oblique muscles, and for centuries the artificial eye has been designed to avoid this ridge.

Analysis of the pattern of the anterior segment of the eye, made as though one were preparing a mold for the contact lens, and of the pattern of the socket after enucleation reveals that but one-half the eye appears to have been removed at the time of enucleation. After a classic enucleation, the artificial eye used to replace the normal eye is less than 12 mm. in thickness, though ample to set well

Fig. 2.—In 1899 Müller made the concave surface of the glass eye bulbous. This was done in conformity with the teaching that the enucleated socket was concave.

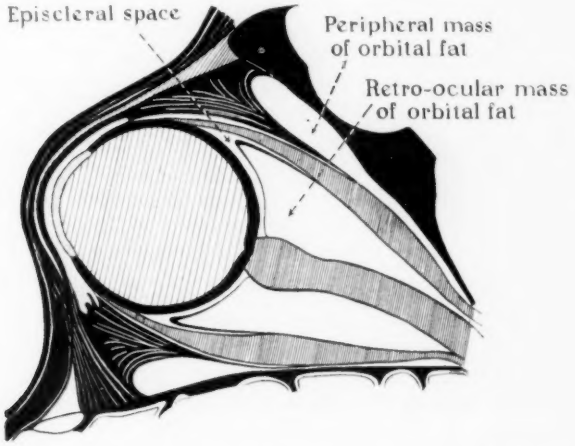

Fig. 3.—Drawing of Tenon's capsule, the fascia and the check ligament, showing how the triangular ligament participates in the formation of the ball and socket joint. The fascia of the muscles is continuous with the check ligament. Though the drawing does not show the oblique muscles, it demonstrates how the superior oblique muscle turns backward at the trochlea, at an angle of 54 degrees. The superior oblique muscle is inserted by fascia into Tenon's capsule and the posterior central portion of the sclera, and the inferior oblique muscle is attached by the fascial sheaths to the posterolateral aspect of the globe.

forward in a position similar to that of the normal eye. The socket, after enucleation, moves forward approximately 12 mm.

If the teachings of René Descartes, the French philosopher, with regard to the physiologic basis for reciprocal innervation, common to opposing muscles, are accepted, then the hypothesis that the oblique and rectus muscles function reciprocally is established.

SEWING OF RECTUS MUSCLES

It is readily demonstrable clinically that improvement, cosmetic or other, does not follow on the sewing of opposing rectus muscles but that, on the contrary, disfigurement of the socket is produced. Closure of the wound in the horizontal plane reduces the upper and the lower cul-de-sac; closure in the vertical plane reduces the lateral cul-de-sac, and the pouch string suture reduces both. Moreover, sewing creates distortion of the fascia. the check ligament and the orbital septum. Most surgeons realize that these things happen. John Green, of St. Louis, repeatedly stated, so I am informed, "that he seldom sewed the wound." His rationale for not doing so may not have been fully explained, but he undoubtedly had a remarkable understanding of the problem. Perhaps he visualized the eyes being wedged into the capsule in ball and socket fashion by the check ligaments and the manner in which these ligaments, the fascia and the capsule were altered by sewing.

The eyelid, in order to open and close, must be supported from beneath as though it were sliding on a fulcrum. Unsupported, the lid's lag is much like a ptosis. It is remarkable to witness how quickly the ptosis is overcome when an artificial eye is inserted into the enucleated socket; the modus operandi is that of the levator palpebrae muscle, which functions and elevates the lid only when its aponeurosis is expanded in archlike form over a fulcrum.

It was the opinion expressed by many authors that the disfigurement of the sulcus following the enucleation could be corrected if a bolster-like cushion was placed atop the prothesis. The crutch of Colomb [17] and that of F. and A. Müller [18] are examples of efforts to accomplish correction of such a fault by physical means. Duke-Elder [7] explained why the physical means made the condition worse instead of better (p. 173).

> The levator palpebrae superioris arises at the apex of the orbit from the lesser wing of the sphenoid above the annulus, its origin blending inferiorly with that of the superior rectus and medially with that of the superior oblique. It runs forwards under the roof of the orbit and upon the superior rectus, the medial borders of the two muscles being adherent by fascial sheaths, and it terminates in an expanded aponeurosis in the upper lid.

Further, it should be recalled that the fascial sheath fuses the levator palpebrae with the superior rectus muscle as they pass to their several insertions. One needs only to pull on the superior rectus muscle after enucleation to produce the characteristic sulcus that follows the operation. One should prevent by any reasonable means the vertical (superior and inferior rectus) muscles from being brought together.

A means of some merit in overcoming the pull on the superior rectus muscle, and indirectly on the levator palpebrae, is to crisscross narrow, undermined bands of conjunctiva between the muscles. Another method is to sew the superior rectus muscle to the levator palpebrae muscle and the tissue about it. However, the best way is to introduce an interim prothesis, such as I have developed. It is made of a transparent plastic with notches at the periphery, one above and one below, to be fitted about the ridge produced by the oblique muscles, and with a large aperture in the center for accomplishing this replacement of tissues and for drainage.

ENUCLEATION VERSUS SUBSTITUTE PROCEDURES

Soon after the simple enucleation had been adopted, its condemnation was heard. As late as 1917 I [19] contributed an article, entitled "Enucleation of the Eyeball A

17. Colomb, P.: United States Government patent 182539, 1905.
18. Müller, F., and Müller, A.: United States Government patent 5183-821, 1912.
19. Dimitry, T. J.: New Orleans M. & S. J. **69**:205, 1916-1917.

Faulty Technic, Cosmetically Considered," and another "Operation Relegating Enucleation of the Eye." [20] Now, with greater knowledge and experience, I advocate what I apparently condemned, my alibi being that the operation I was familiar with at the time of the first writing was an extirpation of the globe, and not an enucleation. Others continue to extirpate, thinking they enucleate the eye.

Mules [21] was the first to register dissatisfaction with the simple enucleation. Instead of getting rid of the globe, he eviscerated the sclera, after having removed the cornea and inserted a glass ball. This was in 1884. In 1920, Grimsdale and Brewerton [8] commented: "This method with slight modification only remains the best cosmetic operation." In time the Mules scleral implant operation met not only with criticism but with condemnation. Nicati,[22] Ray,[23] Hall,[24] Huizinga [25] and I [26] attempted to salvage the Mules procedure. Though these workers removed the source productive of sympathetic ophthalmia, that which condemned it, and made cosmetic improvements in the socket for the artificial eye to rest on, the eye remained immobile. And as the operation was developed to obtain mobility for the prothesis, it lost favor.

I developed a procedure [20] which retained the one-third loss that was required in the Mules operation and did away with the artificial glass eye. I implanted a color ball behind the transparent cornea and demonstrated that the cornea remained transparent, with a pleasing effect, but the cornea thinned to such an extent that it no longer retained the color ball.

The Frost operation [27] should be classed not as a substitute for, but as an adjunct to, simple enucleation. In this operation a 10 to 12 mm. ball is sewn within Tenon's capsule after the globe has been peeled from it. The implanted ball is small, and both the muscles and the capsule are sewn over. Its accomplishment requires that the fascia of the bulb and the muscles, with their attachment to the check ligaments, be drawn on. The operation was performed to restrain the muscles from retracting and in the hope of obtaining a cervix-like stump; however, the muscles normally do not retract, and no such stump is produced.

The body implanted into Tenon's capsule is most commonly spherical. However, there are two exceptions. Berens [28] implants a plastic body in Tenon's capsule which is shaped like a semisphere atop a cone; the apex of the cone sits deep in the cone of the rectus muscles. He wanted to prevent the ball from becoming herniated, as is common when the spherical body is implanted. In the past I have advocated a plastic implant shaped like a semisphere topped by a prism (fig. 4). The prism's ridge, when the plastic body is inserted into Tenon's capsule, faces forward, and the ridge is placed so as to run between the vertical rectus muscles and permits exact sewing of cut edges. The ridge, when the prism atop a semisphere is sewn in the capsule, acts as a horse for the prothesis to rock on, and it has the effect of reducing the disfigurement, such as follows when the superior

20. Dimitry, T. J.: Am. J. Ophth. **2**:653, 1919.

21. Mules, S. H.: Tr. Ophth. Soc. U. Kingdom **5**:200, 1885.

22. Nicati, W.: Arch. d'opht. **232**:347, 1903.

23. Ray, V.: South. M. J. **10**:594, 1917.

24. Hall, E.: Am. J. Surg. **7**:96, 1896.

25. Huizinga, J. G.: Eviscero-Neurotomy: A New Operation, J. A. M. A. **34**:394 (Feb. 17) 1900.

26. Dimitry, T. J.: South. M. J. **10**:594, 1917.

27. Frost, W. A.: Brit. M. J. **1**:1150, 1887.

28. Berens, C.: Am. J. Ophth. **23**:805, 1940.

rectus muscle is pulled on and indirectly pulls on the levator muscle of the upper lid. The first was accomplished, but the artificial eye I had used up to that time would not move.

THE MOBILE PROTHESIS

The ophthalmologist has been diligent in his efforts to obtain a mobile stump; he sought, however, by such means to obtain a mobile prothesis. He has obtained the mobile stump, but he has been unsuccessful in obtaining the mobile prothesis.

Neither the supplemented enucleation procedures nor the substitute operations have advanced the mobile prothesis, and the simple enucleation is found to produce

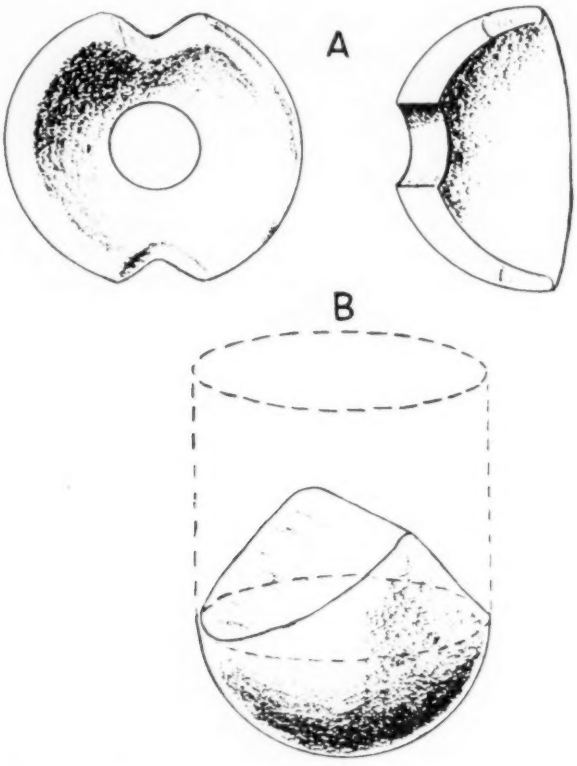

Fig. 4.—*A*, the Dimitry interim prothesis, made of a transparent plastic. It is 23 mm. in diameter and approximately 3 mm. thick. The notches above and below are to hold the muscles apart.

B, the Dimitry semisphere-prism implant is made of a plastic. The parts are of different diameters—10, 11 and 12 mm. When the implant is placed in Tenon's capsule or the sclera, the ridge is pushed forward, and the cut edge of the wound is sutured over it. The ridge runs vertically and holds the vertical rectus muscles parted.

a stump with motion, when calibrated, equal to the motion following the substitute procedures. The problem is not that of tissue mobility but that of the artificial eye.

THE OCULARISTS

The ocularists, artificial eye artisans, had their beginning in ancient days, and America may have led in the ambition to cover a blemish left after the eye was lost. The Incas Indians placed under the lid, to cover a blemish, little stones assembled in mosaic formation.

Paré was the father of surgery, and also the father of the artificial eye (1509-1590). He wrote as follows regarding this:[29]

METHOD OF FITTING AN ARTIFICIAL EYE

I have already treated fully tumors, wounds, ulcers, fractures and dislocations, for which the three functions of surgery are employed, namely: to join what is separated, to remove what is superfluous and to separate what is joined. It remains now to speak briefly of the fourth, which is to supply what is wanting, either through fault of Nature or through accident. . . . One often sees eyes that are deep set, protruding from their sockets or shrunken by reason of a blow or an inflammation. Sometimes when such an accident follows the healing of an ulcer, one can fit an artificial eye, such as the ones shown here, which serves only to improve the appearance of the patient.

Artificial eyes, some of which are shown [in figure 5], are made of enameled gold and are colored like natural eyes.

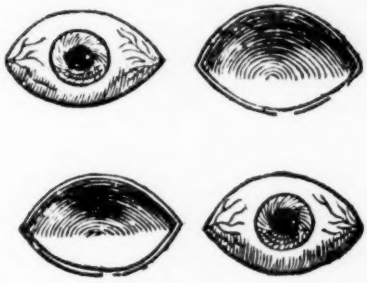

Fig. 5.—Artificial eye of Paré.

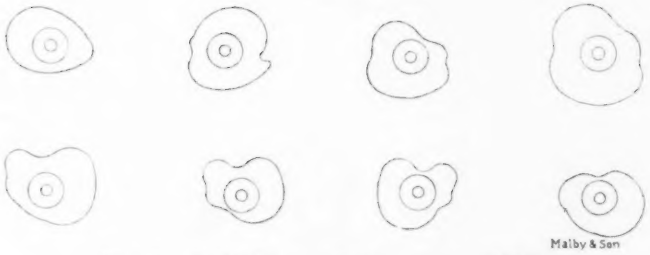

Fig. 6.—Artificial eye of Boissonneau (1854).

Desjardins and Boissonneau,[30] as early as 1866, made Paris the mecca for artificial eyes. Boissonneau was an artisan, not an oculist; Desjardins was an oculist. Boissonneau's[31] artistic ability was communicated to Müller, who, having acquired fully from this source, carried his knowledge back to Germany and capitalized on it.

The original glass eye came from the Greeks of Dalmatia. During the Latin war, after the defeat of the Greeks, the knowledge was taken to Venice and then into Germany. Paré, Desjardins and Snellen were the three with medical knowledge who were interested in the artificial eye.

29. Paré, A.: Les oeuvres de M. Ambroise Paré, conseiller et premier chirurgien du roy, Paris, G. Buon, 1575, book 23, chap. 1.

30. Footnote deleted by author.

31. It was said of Boissonneau, "He traveled the country looking up one-eyed people to fit with his created prothesis."

Jeyes [32] (1892), of England, produced an artificial eye that was to sit forward in the socket and distend the upper lid so that the objectionable ptosis and disfigured sulcus would be corrected. The eye was of enameled metal; to its under belly was attached a spring within a cylinder, the latter provided with a plate to rest on the socket's tissue.

Fig. 7.—Artificial eye of Jeyes (1892).

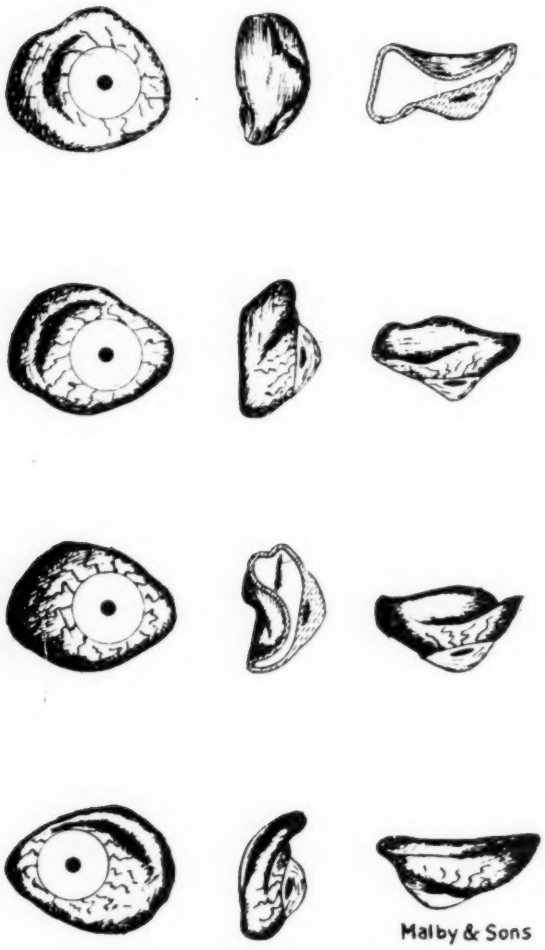

Fig. 8.—Artificial eyes of Müller (1907).

In 1903, the Snellen double shell eye appeared commercially; it was no longer the irritating single shell sunk deep into the socket, but a revision of great ingenuity. It was light in weight and did not retain the heat of the metal eye.

32. Jeyes, P.: United States Government patent, 1892.

Snellen,[33] at the thirteenth international congress in Paris, in 1900, spoke of the glass prothesis he had developed with Müller, of Wiesbaden. He obtained his model by filling the shell eye with gypsum or gutta percha. He mentioned writing to Mr. Müller "for help in manufacturing his newly modeled prothesis." The difficulty of producing the double shell had to be surmounted, and nothing came of the work. Later, advance was made, and in 1896, after the Heidelberg Ophthalmological Congress, as he stated: "I called to see Mr. Müller, at which time we discussed the difficulty in blowing the double shell wall without breaking the globule." In September, his efforts were rewarded and the Snellen *reform Auge* (D. R. G. M. no. 107044) was produced. As a result of this new design, the sinking of the upper lid, which follows enucleation and continues to be commented on by the public in those wearing the shell eye, was corrected, and less irritation of the conjunctiva was noted. However, the design proved a failure with regard to mobility.

In the United States, Davis of New York was probably the first to design an artificial eye of glass. The Boissonneau eye in this country was first made by Pierre Gougelman. The founder of the Müller firm established its business under the names *Cartel Uri* and *Cartel Ocar*. The two cartels became one, and subsequently the most famous in Continental Europe.

Traveling ocularists today, as during Boissonneau's time, go about fitting artificial eyes. They make an artificial eye which duplicates exactly the color of the iris and design it to sit more comfortably in the socket than does the stock eye. They crack the globule to be longer in the horizontal than in the vertical direction and provide it with the same shape as that given it through the centuries (figs. 5, 6 and 7). This was done to prevent its wandering from a fixed setting. Its exact fixation provides against any desultory motion that the stump may produce.

Snellen, the great ophthalmologist of Holland, has been the only one throughout the centuries to meet the need of an artificial eye to sit forward in the socket as does the normal eye; however, he was not able to remove the *bête noire,* for today, as in ancient days, the eye is but a shield anchored in position.

It was not the ocularists alone who were at fault, but the material with which they were compelled to work, for kryolith glass, which had brought so much happiness to the afflicted in that it could be readily blown and beautifully colored, defeated the ideal the surgeon sought, namely, mobility for the prothesis. The very nature of glass, that of fragility, took it out of the hands of the person best qualified to adjust through knowledge of anatomy and physiology, the ophthalmologist himself, and placed it in the hands of persons with but a modicum of knowledge in the basic science.

The ophthalmic surgeon hardly dared touch the artificial eye for fear of breaking it. Since he did not know how to blow glass, there was nothing he could do; he had as yet no substitute products for making artificial eyes, and the material at his disposal was unalterable.

The surgeon was also at fault, for he commonly did not make a proper enucleation, nor did he grasp the teaching of Cleoburey: The socket left after enucleation is of a standard pattern; so the artificial eye is to be standardized.

THE PLASTIC ARTIFICIAL EYE

Plastics have provided an opportunity for the ophthalmologist to interest himself in a problem he has neglected, viz., his designing the prothesis instead of leaving it to those who fit artificial eyes. He neglected his responsibility when he failed to see that the prothesis is shaped so that it may move. The prothesis

33. Snellen, P.: Cong. internat. de méd., Rap. sect. d'opht. (pt. 2) **1**:27, 1900.

of the artisan was designed to thwart movement whereas the surgeon labored to make possible movement of the prothesis that thwarted motion.

The plastic eye permits alterations—it can be cut, sawed and sanded. It is not readily acted on by the tears, nor does the heat of the body affect it. It can be dropped without being broken. It may be sterilized, whereas the glass eye is a *noli me tangere.*

CONCLUSION

Historians, anatomists, physiologists, ophthalmologists, physicists and ocularists have contributed to a series of errors, which are indicated here.

Cleoburey replaces Ferrall and Bonnet in priority for the procedure of enucleation. Tenon is replaced by the ancients. The check ligaments not only hold the rectus muscles in check but act reciprocally to them. They help pull the tissues forward when the rectus muscles are cut. Besides, they function as a wedge to complete the ball and socket joint in which the eye may rotate.

The tissues of the socket come forward, particularly after an enucleation, as a result of the action of the oblique muscles the check ligaments and the elastic fibers of the capsule of Tenon. Peeling of the eye from Tenon's capsule is enucleation; nothing else is. The enucleation procedure was perfect from its first development. Imperfect procedures were the result of conjectures rather than of study of facts. The socket of enucleation is not concave.

Though the glass eye is a gem, it does not satisfy the exacting patient, who wants it set not in the rim of the bony orbit but like the orb in the orbit, so that it may move. The use of plastics solves the problem, and the ophthalmologist may now direct the making of the artificial eye of the future and see that it is properly tailored.

4325 St. Charles Street.

EFFECT OF LOCAL ANESTHETICS ON REGENERATION OF CORNEAL EPITHELIUM

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AND
LIEUTENANT SUMNER D. LIEBMAN
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Our purpose in the present investigation was to determine experimentally the effect of various local anesthetics on the regeneration of corneal epithelium. Clinically it has been observed from time to time that local anesthetics have an inhibitory influence on the regeneration of corneal epithelium. In 1902 Fuchs,[1] for this reason, stated that patients should be prohibited from using cocaine at home for the treatment of corneal abrasions. Many of the newer anesthetics are, however, said to be innocuous. Stallard [2] stated that tetracaine has no toxic effect on the regenerating epithelium. According to Gifford,[3] 0.5 per cent butacaine sulfate or phenacaine hydrochloride causes little or no damage to the epithelium and may be used several times a day. Heretofore no attempt has been made to determine experimentally whether or not local anesthetics affect the regrowth of corneal epithelium.

METHOD

Guinea pigs (4 for the study of each drug) were used as test animals, since they are easily handled.[4] The animals were anesthetized by intraperitoneal injection of pentobarbital sodium.

The drugs used in these experiments were fresh preparations similar to those in daily use in the clinic of the Massachusetts Eye and Ear Infirmary. These drugs were solutions of 10 per cent cocaine hydrochloride, 4 per cent cocaine hydrochloride, 1 per cent butacaine sulfate, 4 per cent larocaine hydrochloride, 1 per cent phenacaine hydrochloride and 0.5 per cent tetracaine hydrochloride, all containing 0.5 per cent chlorobutanol. One per cent phenacaine hydrochloride and 0.5 per cent tetracaine hydrochloride in ointment form [5] were instilled into the right eyes of two other groups of guinea pigs. The left, or control, eyes of these animals were treated with ointment base containing no local anesthetic. The experiments for the 10 per cent cocaine hydrochloride and the 1 per cent phenacaine hydrochloride were carried out in duplicate series, and the eyes of the second series of animals were removed at varying intervals for histologic examination.

From the Howe Laboratory of Ophthalmology, Harvard University, and the Massachusetts Eye and Ear Infirmary.

Read at the annual meeting of the Massachusetts Alumni Association before the Ophthalmological Section, Boston, Jan. 21, 1942.

1. Fuchs, E.: Ueber Cocaine, Wien. klin. Wchnschr. **15**:962, 1902.

2. Stallard, H. O., in Ridley, F., and Sorsby, A.: Modern Trends in Ophthalmology, London, Butterworth & Co., Ltd., 1940, chap. 49, p. 543.

3. Gifford, S. R.: A Handbook of Ocular Therapeutics, Philadelphia, Lea & Febiger, 1942, pp. 24 and 378.

4. Cats and rabbits were also used, but the results obtained were equivocal. It was thought that the nictitating membrane interfered with equal distribution of the drug on the cornea. Identical abrasions, 2 mm. wide, were made with a metal spatula in the two eyes, from limbus to limbus, across the centers of the corneas. The lesions were immediately stained with 2 per cent fluorescein sodium to make sure that equal areas had been abraded in the two corneas. The right eye of each animal was treated with the drug under investigation every hour day and night until both eyes showed no staining or until an unequivocal result had been obtained. Usually nothing was instilled into the left eye. The corneas were stained at various intervals, as indicated on the accompanying charts, and for comparative purposes the staining areas were recorded.

5. The ointment base consisted of 3 per cent oxycholesterol in petrolatum.

Further studies were carried out to evaluate the influence of tonicity of the cocaine and the tetracaine solutions on the regeneration of corneal epithelium. Six groups of guinea pigs (4 animals in each group) were used. The right eyes of one group were treated with a 4 per cent solution of cocaine hydrochloride (hypotonic to tears). The right eyes of a second group were treated with a solution containing 4 per cent cocaine hydrochloride and 1.25 per cent sodium chloride (roughly isotonic to tears). The right eyes of a third group were treated with a solution containing 4 per cent cocaine hydrochloride and 5 per cent sodium chloride (hypertonic to tears). The remaining three groups of animals were treated in a similar manner, but 0.5 per cent tetracaine hydrochloride was substituted for 4 per cent cocaine hydrochloride. The left, or control, eyes of all the animals were treated with distilled water (hypotonic solution), 1.25 per cent sodium chloride (isotonic solution) and 5 per cent sodium chloride (hypertonic solution). All solutions contained 0.5 per cent chlorobutanol.

Since the p_H of fresh stock 4 per cent solutions of cocaine hydrochloride used in the preceding experiment was about 4, a separate study was carried out to determine whether or not the inhibitory effect was due to this relatively low p_H. The influence of the p_H alone was studied by the use of potassium acid phthalate as buffer (without an anesthetic) at p_H 2.82, 4.12 and 6.28. The effect of each solution was tested by hourly instillations into the right eyes of 3 guinea pigs. The left, or control, eyes were untreated.

The effect of each anesthetic on the intact epithelium was tested in the usual manner by hourly instillations in the eyes of normal guinea pigs.

RESULTS

The results obtained with the solutions of the various local anesthetics are summarized in the accompanying charts. The areas which stained with the fluorescein are represented in black. The dotted lines indicate the extent of the initial lesions.

Ten Per Cent Cocaine Hydrochloride.—On the third day all treated eyes showed pronounced swelling of the stroma on slit lamp examination, and on the fourth day several of the corneas presented a superficial pannus. Treatment was discontinued at this time, and the eyes of 1 animal (93) were enucleated for histologic study. Two weeks later the treated eyes of the remaining animals appeared normal except for a small, deep central corneal opacity. Obviously 10 per cent cocaine hydrochloride appreciably retarded the regeneration of epithelium (chart 1 *A*).

Four Per Cent Cocaine Hydrochloride.—The right eyes of animals in this group were treated with an aqueous solution of 4 per cent cocaine hydrochloride. Chart 1 *B* shows that the regeneration of corneal epithelium was definitely delayed by this anesthetic, although the effect was not quite so pronounced as that with the 10 per cent solution. In the treated eyes a superficial pannus did not develop, as was observed in all eyes treated with 10 per cent cocaine hydrochloride.

Effect of Variation in Tonicity of 4 Per Cent Cocaine Hydrochloride.—Chart 1 *B, C* and *D* gives the results of these studies. It can be seen that the inhibitory effect diminished as increasingly hypertonic solutions were used.

Tetracaine Hydrochloride, 0.5 Per Cent.—This anesthetic was studied in the same manner as was 4 per cent cocaine hydrochloride, with results which, as can be seen in chart 2 A, were qualitatively similar. The inhibitory effect on the regeneration of epithelium, while not so striking as that of cocaine, was nevertheless present.

Effect of Variation in Tonicity of 0.5 Per Cent Tetracaine Hydrochloride.—Chart 2 *A, B* and *C* shows that with increasing tonicity the inhibitory effect of 0.5 per cent tetracaine hydrochloride was almost eliminated.

Other Anesthetics.—The delayed healing of the epithelium was observed in varying degrees with 1 per cent phenacaine hydrochloride, 1 per cent butacaine sulfate and 4 per cent larocaine hydrochloride (chart 2 *D, E* and *F*). As can be seen in these portions of the chart, 1 per cent phenacaine hydrochloride and 0.5 per cent tetracaine hydrochloride were the least toxic to the regenerating epi-

thelium. One per cent butacaine sulfate, 4 per cent larocaine hydrochloride, 4 per cent cocaine hydrochloride and 1 per cent cocaine hydrochloride showed an increasingly inhibitory effect, in the order named. Five-tenths per cent tetracaine hydrochloride and 1 per cent phenacaine hydrochloride in ointment base gave results similar to those of aqueous solutions of these drugs, and the data are not included.

Effect of the p_H.—It was found that the solution which buffered at a p_H of 2.82 with no anesthetic had a definite inhibitory effect on the regeneration of the corneal

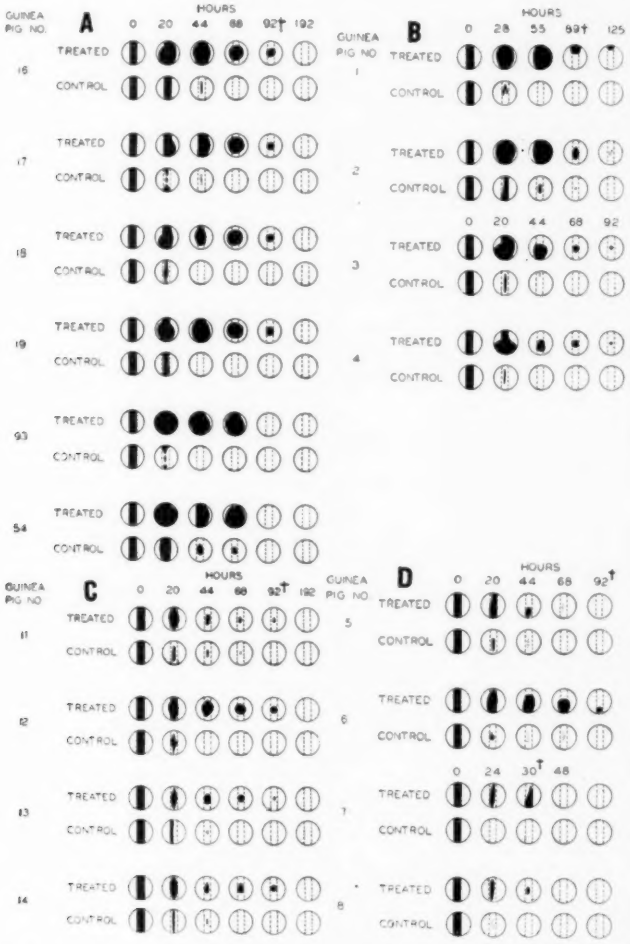

Chart 1.—Effects of 10 and 4 per cent cocaine hydrochloride on the regeneration of corneal epithelium. The areas which stained with fluorescein are represented in black. The dagger (†) indicates the time at which treatment was discontinued. *A* represents results with 10 per cent cocaine hydrochloride; *B*, with 4 per cent cocaine hydrochloride in hypotonic solution of sodium chloride; *C*, with 4 per cent cocaine hydrochloride in isotonic solution of sodium chloride, and *D*, with 4 per cent cocaine hydrochloride in hypertonic solution of sodium chloride.

epithelium, whereas the solutions with a p_H of 4.12 and 6.28 had no effect. None of the anesthetic solutions used had a p_H of less than 4 when freshly prepared. Moreover, the anesthetic solutions used in the aforedescribed experiments were not buffered and probably became somewhat less acid when brought into contact with

the cornea and tears. It is concluded, therefore, that the aforedescribed results were not dependent on the p_H of the solutions.

Effect of Local Anesthetics on Intact Epithelium.—Ten and 4 per cent solutions of cocaine hydrochloride instilled hourly into the intact eyes of guinea pigs produced areas on the corneas which stained with fluorescein. The other anesthetics did not produce staining areas.

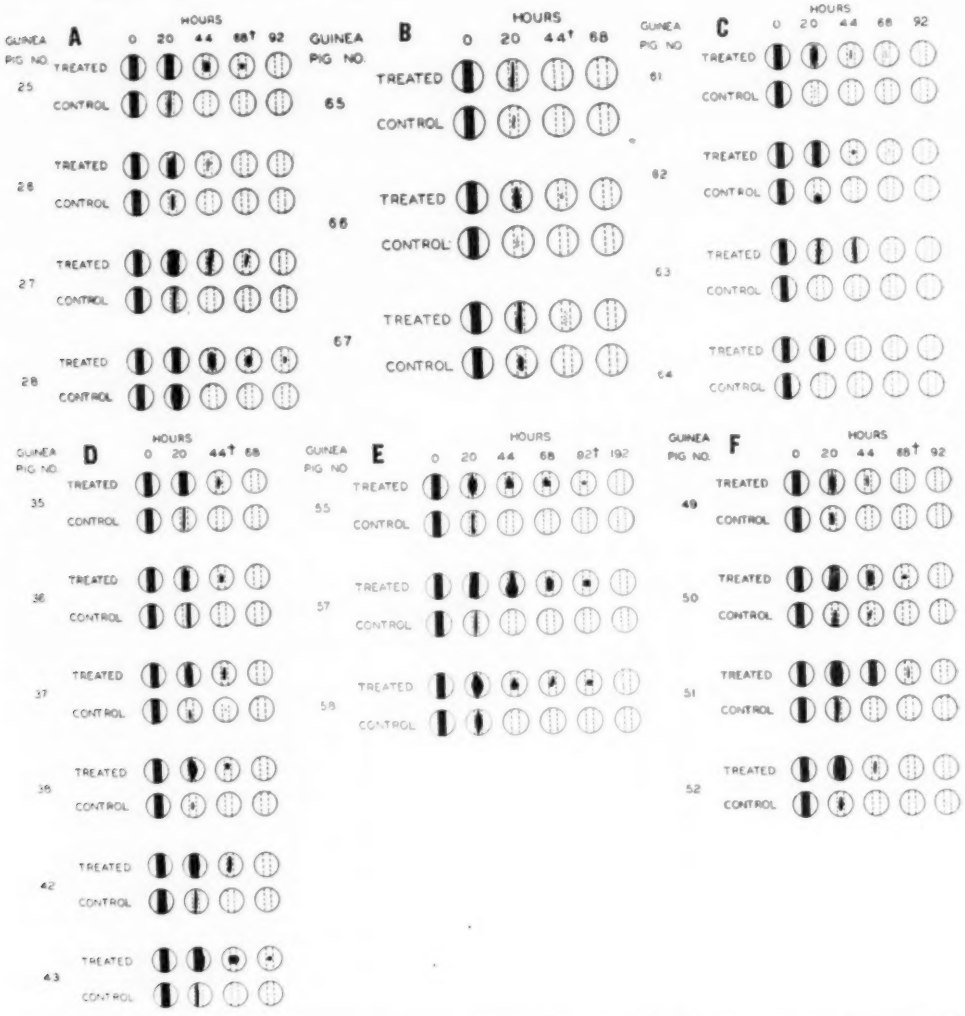

Chart 2.—Effect of 0.5 per cent tetracaine hydrochloride and various other local anesthetics on the regeneration of corneal epithelium. The method of recording is the same as that used in chart 1. *A* represents results with 0.5 per cent tetracaine hydrochloride in hypotonic solution of sodium chloride; *B*, with 0.5 per cent tetracaine hydrochloride in isotonic solution of sodium chloride; *C*, with 0.5 per cent tetracaine hydrochloride in hypertonic solution of sodium chloride; *D*, with 1.5 per cent phenacaine hydrochloride; *E*, with 4 per cent larocaine hydrochloride, and *F*, with 1 per cent butacaine sulfate.

Pathologic Studies.—Pathologic studies were made on two groups of animals, one treated with 10 per cent cocaine hydrochloride and the other with 1 per cent phenacaine hydrochloride. The eyes were sectioned perpendicular to the long axis

of the abrasion, and the control eyes, or left, were compared with the treated eyes. The latter showed loss of cellular boundaries, with pale, swollen nuclei in the cells which bounded the abrasion. These differences were progressively more pronounced in the animals which had received longer treatment. Mitotic figures were difficult to find in either the treated or the control eyes. The epithelium bounding the abrasions in the untreated eyes looked more normal, having visible cell boundaries and nuclei. In some of the eyes treated with 10 per cent cocaine hydrochloride there were leukocytic infiltration of the stroma and polymorphonuclear cells on the endothelium and in the anterior chamber. The series treated with phenacaine showed no such inflammatory reaction, although there were varying degrees of swelling of the corneal stroma beneath the abrasions.

SUMMARY

It can be seen from the results described that all of the local anesthetics tested had some delaying effect on the healing process of the corneal epithelium of the guinea pig. This effect is modified in degree by the concentration and the tonicity of the anesthetic agent. The p_H is probably not a determining factor, since buffered solutions at a p_H comparable to that of the anesthetics used showed relatively little inhibitory action. Of the various anesthetics tested, 1 per cent phenacaine hydrochloride and a hypertonic 0.5 per cent solution of tetracaine hydrochloride were the least toxic to the regenerating epithelium.

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BINOCULAR REFRACTION WITH CROSS CYLINDER TECHNIC

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It is a well known fact that many persons who wear corrective lenses the prescription for which has been determined by accurate monocular refraction and who do not have abnormal lateral or vertical phorias are uncomfortable during binocular vision. In many cases the trouble is due to changes in the axes of cylinders when both eyes are used together for distant vision and during convergence accommodation. Several test methods have been devised to determine these changes; yet no cases were reported prior to those of Hughes,[1] in 1941. It is the purpose of this paper to analyze the changes in the axis of astigmatism under varying conditions in a small series of 70 normal eyes with astigmatism of 1.00 D. or more and to introduce the use of the cross cylinder to determine these changes under binocular fixation. All these eyes were those of patients with binocular single vision. As shown in the table, the axes were determined monocularly during and after cycloplegia for 20 feet (6 meters) and binocularly for both 20 feet and 10 inches (25 cm.). In all instances the changes were checked several times to minimize errors. Thirty-three of the 70 eyes had some changes in axis. Twenty-four varied in monocular axis during and after cycloplegia. Only 4 showed variations between the monocular and the binocular axis at 20 feet. Fourteen eyes had changes between the binocular axis at 20 feet and that at 10 inches.

The cause of the shift in axis under varying conditions has been discussed extensively. The shift from the cycloplegic to the postcycloplegic monocular axis for fixation at 20 feet may be explained by slight changes in the position of the crystalline lens. It has been suggested that the shift may be due to aberrations produced by the outer zone of the cornea when the pupil is dilated. That this is untrue was suggested by the fact that the axis did not change when a disk with a hole 3.5 mm. in diameter was placed behind the lenses in the trial frame. The change from monocular to binocular conditions and the changes associated with convergence accommodation are not as easily explained. Four theories have been advanced. The first is that lenticular changes cause the shift in the axis. Hughes, in a report of 4 cases in which the axis of astigmatism changed on accommodation, concluded that "the change in axis could not be due to rotation of the eye as a whole, as no abnormal tension was seen with the unaided eye, with the microscope or with the ophthalmometer. The phenomenon must therefore be lenticular in origin." The second theory is that a fusional compensation occurs (Verhoeff [2]), which results in a slight shift in axis. The third theory is that of torsional movements of the globe (cyclophoria). This has been championed by Savage. A fourth theory, advanced by Pascal,[3] is that the action of the extrinsic muscles in near vision slightly changes the curves of the cornea.

From the Eye Clinic, Barnes General Hospital, Vancouver, Wash.

1. Hughes, W. L.: Change of Axis of Astigmatism on Accommodation, Arch. Ophth. **26**:742 (Nov.) 1941.

2. Verhoeff, F. H.: Description of a Reflecting Phorometer, Am. J. Physiol. Optics **7**:39, 1926.

3. Pascal, J. I.: The Axis of Astigmatism, Arch. Ophth. **27**:189 (Jan.) 1942.

As a result of the observations in the present series of cases, it appears that each theory may have its place in the explanation of the various shifts. Change in position of the lens most reasonably explains the difference in the monocular axes during and after cycloplegia. Fusional compensations may explain the change in axis from monocular to binocular conditions when the subject is fixing at 20 feet. The change in axis from distance to near vision during binocular fixation appears to be most reasonably explained by torsional changes. That this is at least possible is suggested by the observations in a case of persistent postoperative paradoxic diplopia with horror fusionis. A soldier aged 23 had begun to show squint at the age of 22 months. In 1936 the squint was corrected surgically, but diplopia resulted. He was able to tolerate the diplopia with a correction of 3 prism

Changes in Axis of Cylinders

Case No.	Age, Yr.	Right or Left Eye	Strength of Cylinder	20 Feet (6 Meters)			10 Inches (25 Cm.)
				Axis Under Cycloplegia	Monocular Axis, Post-cycloplegic	Binocular Axis, Post-cycloplegic	Binocular Axis, Near Vision
1	34	R	+1.12	110	117	117	120
2	24	R	+1.50	170	170	170	175
3	24	L	+1.50	10	10	10	5
4	23	R	+2.00	100	100	100	95
5	24	R	+1.12	90	87	87	87
6	24	L	+1.00	90	87	87	87
7	25	R	+1.00	140	140	140	135
8	41	R	+1.00	...	110	110	115
9	37	R	+2.00	107	107	107	102
10	44	R	+1.25	85	88	85	90
11	32	R	+1.50	15	10	10	10
12	29	L	+1.12	65	50	50	50
13	30	L	+1.12	97	100	100	100
14	43	L	+1.25	..	145	145	140
15	24	R	+2.50	110	110	110	115
16	24	L	+1.50	53	57	57	57
17	20	R	+2.00	100	95	95	95
18	20	L	+1.62	80	75	75	75
19	21	R	+1.25	105	114	114	114
20	30	R	+1.37	172	165	165	165
21	30	L	+1.87	160	165	165	165
22	28	R	+1.75	100	105	105	105
23	28	L	+1.00	65	65	65	70
24	38	L	+2.00	80	86	86	86
25	30	R	+1.75	115	110	110	110
26	41	R	+2.75	116	110	110	110
27	22	L	+2.00	90	95	95	95
28	21	R	+2.00	90	75	75	75
29	40	R	+3.50	177	5	180	180
30	22	R	+1.25	35	35	30	35
31	24	L	+1.00	77	82	82	82
32	44	R	+1.37	47	43	47	52
33	44	L	+1.00	150	155	155	160

diopters base in before each eye, 2 prism diopters base up before the right eye and 2 prism diopters base down before the left eye. The images were then as close together as possible. For near vision, however, the prisms had to be rotated nasalward, 82 and 172 degrees for the right eye and 107 and 17 degrees for the left eye in order to make the patient comfortable.

Of the many methods [4] which have previously been used to determine the astigmatic axis under binocular fixation, some require special apparatus, such as the Leland refractor,[5] which uses polaroid filters, while another utilizes two separate charts with a long septum between them, placed so that each eye of the patient sees a separate chart. One may use a neutral density filter or a + 2.00 D. sphere (Copeland) or a multiple pinhole disk before the eye not being tested. Still

4. Copeland, J. C.: Locating the Astigmatic Axis Under Binocular Fixation, in Ten Years of Optical Developments (November 1940), Chicago, Riggs Optical Company, 1942.

5. van Wien, S.: The Leland Refractor: Method for Refraction Under Binocular Conditions, Arch. Ophth. **23**:104 (Jan.) 1940.

another test is based on dissociation of a single line of test letters with a 6 D. vertical prism. The objection to the latter tests is that there is definite dissociation of the two eyes and true binocular function is not tested.

For the past four years I have used the cross cylinder (+ 0.25 D.; — 0.25 D.) for determination of the axis of cylinders binocularly for distance, and more recently I have employed it to determine the axis of astigmatism binocularly for near vision when reading glasses alone were ordered. In explaining the method I shall first discuss briefly my refractive procedure with cycloplegia and at the postcycloplegic examination.

After careful retinoscopy with cycloplegia, plus cylinders only being used, the lenses representing the net retinoscopic findings are placed in the trial frame, with the eye not under examination covered. The spherical correction is modified as necessary, the smallest test letters visible, usually the 20/20 line, being used. Frequently when a small amount of residual accommodation is present, the patient prefers the addition of a — 0.25 D. sphere. If another + 0.25 D. sphere is held before the lens combination and the patient prefers it, the — 0.25 D. sphere was accommodative and should be removed. When the best spherical correction has been obtained, the axis of the cylindric correction is determined with the cross cylinder. The 20/50 or the 20/70 test letters are now used. The details of the use of the cross cylinder for axis and strength have been well described by Crisp [6] and others.

The strength of the cylinder in the trial frame is modified by placing the plus and minus axes of the cross cylinder alternately in front of the trial case cylinder with the axes parallel. The cross cylinder indicates not the amount of cylinder to be added or subtracted but only the direction of change. Changes of 0.12 D. are used. If a + 1.00 D. cylinder is in the trial frame at axis 90 and more letters are seen, or are better seen, with the minus position of the crossed cylinder, a — 0.12 D. cylinder is added to the cylinder in the frame. The cross cylinder is again placed alternately in the minus and in the plus position before the lens, and the best position is determined. If the plus position is favored, the correct cylinder is one between + 0.87 and + 1.00 D. The one preferred by the patient is to be used. It is usually the former. To be certain, the simple cylinders alone with 20/20 or 20/15 test letters are again used. If the minus position is favored, another — 0.12 D. cylinder is added until the plus position is favored. If a + 1.00 D. cylinder is in the trial frame at axis 90 and more letters are seen with the plus position of the cross cylinder, a + 0.12 D. cylinder is added to the cylinder in the frame. The cross cylinder is again used, and the favored position is determined, whether plus or minus. If the minus position is favored, the correct cylinder is one between + 1.00 and + 1.12 D. The former is usually ordered. If the plus position is favored, another + 0.12 D. cylinder is added until the minus position is favored.

When the correct strength and axis of the cylinder are determined, the smallest visible test letters are again used, usually the 20/20 or the 20/15 line. Changes in the sphere are now made. Changes of 0.12 D. should be made where recognized.

The same procedure is carried out monocularly for the other eye.

At the postcycloplegic examination all testing is done binocularly. First, the total sphere is reduced equally as necessary or as indicated. Then the cross cylinder test for axis should be made first on one eye and then the other, with

6. Crisp, W. H.: The Cross-Cylinder Tests Especially in Relation to the Astigmatism Axis, Tr. Ophth. Soc. U. Kingdom **60**:495, 1931.

the patient using both eyes. No attempt is made to suspend the vision of the eye which is not under refraction. In cases in which spectacles with high cylinders are ordered for near vision only, the same procedure should be used for the axis of each cylinder, with both eyes open, the patient fixing on test material in the position of ordinary reading. The smallest Snellen and Jaeger test types must be used for distance and near vision respectively. The strength of cylinder is not usually changed except when glasses are ordered for the first time in cases of high cylindric errors and in cases of anisometropia, conical cornea, corneal opacities or eccentric pupil.

When manifest refractions are made with the cross cylinder, the best sphere must be determined before cylindric changes are made, as was pointed out by Jackson.[7] Recently Williamson-Noble [8] showed that if a patient is fogged he tends to choose too strong a cylinder against the rule, whereas in the opposite condition, when hyperopia is undercorrected or myopia is overcorrected, he tends to choose too strong a cylinder with the rule. This is based on the fact that blurred letters are more easily recognized when their vertical components are in better focus then when the horizontal ones are clearer. Copeland [9] expressed the belief that the use of the cross cylinder under a slight fog leads to fallacious results, since the dioptric midpoint is moved and symmetric comparison is lost when pivoting around the false midpoint.

After the best sphere is determined in manifest refraction, the cross cylinder is first used in the 90 and in the 180 axis, and either plus or minus cylinder is added, in the indicated axis. Individual preference must be considered as to whether a plus or a minus cylinder is used. As soon as a 0.25 D. cylinder is found, the axis is determined as previously described, and further changes in axis strength are made. When the total astigmatic correction has been found, the axis should be rechecked. If any amount of cylinder is found, the sphere must be changed in an amount equal to half the cylinder and opposite it in sign. It should be changed with each 0.25 or 0.5 D. of cylinder. If + 0.25 D. of cylinder is added, half this amount, or 0.12 D., should be subtracted from the sphere. In many cases in which a considerable amount of cylinder is present, the changes in sphere may be made with each 0.5 D. of change in cylinder and the 0.12 D. sph. changes made at the end point. This procedure follows the principle of spherical equivalents. Because this principle is important in cross cylinder refraction, and also in the obtaining of comfortable binocular vision in cases of anisometropia, a brief résumé of its use in the latter will not be amiss. Copeland [10] introduced this principle in 1928. It had been employed by designers of ophthalmic lenses in attempts to establish the correct base curve for the reduction of marginal astigmatism in compound lenses. In the ophthalmologic journals the subject has been discussed only by Prangen.[11]

The spherical equivalent of a compound lens system is located at the midpoint between the two principal meridians of the lens system. In other words, it is

7. Jackson, E.: How to Use the Cross Cylinder, Am. J. Ophth. **13**:321, 1930.

8. Williamson-Noble, F. A.: Possible Fallacy in the Use of the Cross-Cylinder, Brit. J. Ophth. **27**:1, 1943.

9. Copeland, J. C.: Personal communication to the author.

10. Copeland, J. C.: A Study in the Application of Cylindric Corrections, Optom. Weekly **19**:191 (April 5) 1928; in Ten Years of Optical Development, Chicago, Riggs Optical Company, 1942: An Important Diagnostic Point in the Correction of Astigmatism, May-June 1931; Analysis and Use of the Crossed Cylinder, September 1931.

11. Prangen, A. de H.: The Significance of Sturm's Interval in Refraction, Am. J. Ophth. **24**:413, 1941; Some Problems and Procedures in Refraction, Arch. Ophth. **18**:432 (Sept.) 1937.

the circle of least confusion located at the dioptric midpoint of the interval of Sturm. The term "spherical equivalent" is somewhat loosely used. Perhaps the terms "spherical mean" or "spherical average" would be better.[9] Numerically, the spherical equivalent of a compound lens system is equal to the spherical power of the system plus half the power of the cylinder. The spherical equivalent of a simple cylinder is equal to half the power of the cylinder. The following cases exemplify the principle.

CASE 1.—Private E. W., aged 23 (chart 1).

Refraction with 5 per cent homatropine hydrobromide cycloplegia gave the following results:

Right eye: —2.75 D. sph. ⊂ +2.00 D. cyl., axis 100
Left eye: —1.50 D. sph. ⊂ +0.25 D. cyl., axis 90

At postcycloplegic examination this correction gave normal visual acuity of 20/20 for each eye, but caused severe discomfort binocularly.

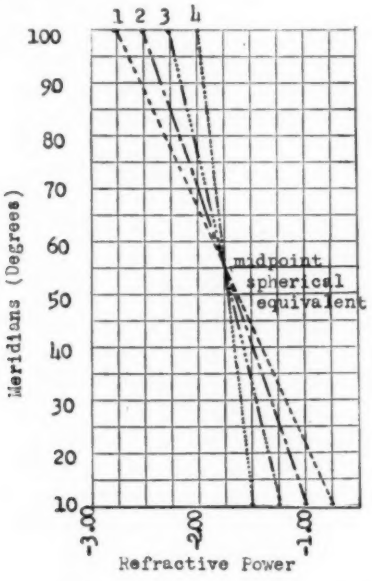

Chart 1.—Schematic representation of lens combinations with the same spherical equivalent as that used in case 1. Combination 3 was preferred.

1. —2.75 D. sph. ⊂ +2.00 D. cyl., axis 100 (full correction)
2. —2.50 D. sph. ⊂ +1.50 D. cyl., axis 100
3. —2.25 D. sph. ⊂ +1.00 D. cyl., axis 100
4. —2.25 D. sph. ⊂ +0.50 D. cyl., axis 100

The spherical equivalent rule was used to determine the various lens combinations that could be used for the right eye without disturbance of the position of the optical midpoint, as shown in chart 1. The rule is as follows: In reduction of a cylinder, half the reduced amount is added to the sphere, the sign of the cylinder being maintained during the addition.

1. —2.75 D. sph. ⊂ +2.00 D. cyl., axis 100 (full correction)
2. —2.50 D. sph. ⊂ +1.50 D. cyl., axis 100
3. —2.25 D. sph. ⊂ +1.00 D. cyl., axis 100 (preferred)
4. —2.00 D. sph. ⊂ +0.50 D. cyl., axis 100

These combinations were tried in the order listed, beginning with the stronger cylinders. The patient can easily tell whether the combination is comfortable within a few minutes. The most comfortable combination may be tried in a trial frame in the waiting room for a

half-hour as a test. In this particular case the third combination gave comfort and was prescribed. Visual acuity with this system was 20/25.

CASE 2.—Private J. D. N., aged 21 (chart 2).

Refraction with 5 per cent homatropine hydrobromide cycloplegia gave the following results:

Right eye: —4.00 D. sph. ⌒ + 2.75 D. cyl., axis 110
Left eye: —0.50 D. sph. ⌒ + 1.00 D. cyl., axis 90

The lens combinations tried were:

1. —4.00 D. sph. ⌒ + 2.75 D. cyl., axis 100 (full correction)
2. —3.75 D. sph. ⌒ + 2.25 D. cyl., axis 100
3. —3.50 D. sph. ⌒ + 1.75 D. cyl., axis 100
4. —3.00 D. sph. ⌒ + 1.25 D. cyl., axis 100 (preferred)
5. —2.75 D. sph. ⌒ + 0.75 D. cyl., axis 100

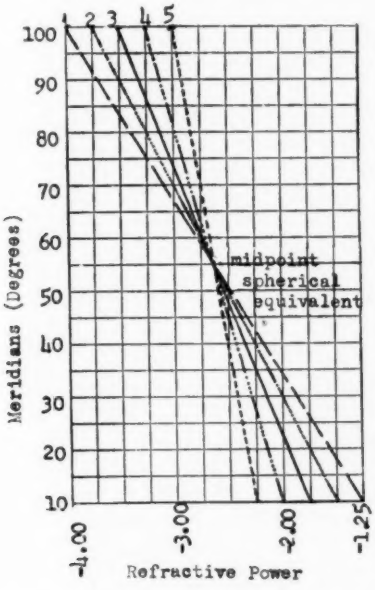

Chart 2.—Schematic representation of lens combinations with the same spherical equivalent as that used in case 2. Combination 4 was preferred.

1. —4.00 D. sph. ⌒ + 2.75 D. cyl., axis 100 (full correction)
2. —3.75 D. sph. ⌒ + 2.25 D. cyl., axis 100
3. —3.50 D. sph. ⌒ + 1.75 D. cyl., axis 100
4. —3.25 D. sph. ⌒ + 1.25 D. cyl., axis 100
5. —3.00 D. sph. ⌒ + 0.75 D. cyl., axis 100

The prescription preferred was:

Right eye: —3.00 D. sph. ⌒ + 1.25 D. cyl., axis 100
Left eye: —0.50 D. sph. ⌒ + 1.00 D. cyl., axis 90

CASE 3.—Private G. W. A., aged 28 (chart 3).

Refraction with 5 per cent homatropine hydrobromide cycloplegia gave the following results:

Right eye: + 4.00 D. sph. ⌒ + 1.00 D. cyl., axis 95 (20/20 vision)
Left eye: + 3.00 D. sph. ⌒ + 3.25 D. cyl., axis 75 (20/20 vision)

Sphere cut for each eye was + 1.75 D.

The lens combinations tried with the left eye were as follows:

1. + 1.25 D. sph. ⊂ + 3.25 D. cyl., axis 75
2. + 1.50 D. sph. ⊂ + 2.75 D. cyl., axis 75
3. + 1.75 D. sph. ⊂ + 2.25 D. cyl., axis 75
4. + 2.00 D. sph. ⊂ + 1.75 D. cyl., axis 75 (preferred)
5. + 2.25 D. sph. ⊂ + 1.25 D. cyl., axis 75

The prescription preferred was:

Right eye: + 2.25 D. sph. ⊂ + 1.00 D. cyl., axis 95
Left eye: + 2.00 D. sph. ⊂ + 1.75 D. cyl., axis 75

CASE 4.—Private B. B. I., aged 20 (chart 4).

Refraction with 5 per cent homatropine hydrobromide cycloplegia gave the following results:

Right eye: + 1.50 D. sph., axis 90
Left eye: — 2.50 D. sph. ⊂ + 3.50 D. cyl., axis 105

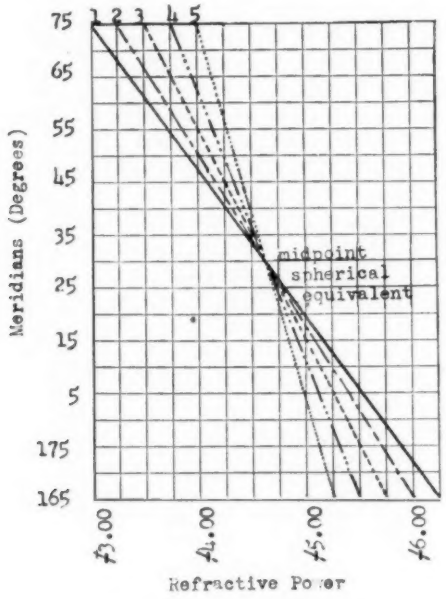

Chart 3.—Schematic representation of lens combinations with the same spherical equivalent as that used in case 3. Combination 4 was preferred.

1. + 3.00 D. sph. ⊂ + 3.25 D. cyl., axis 75 (full correction)
2. + 3.25 D. sph. ⊂ + 2.75 D. cyl., axis 75
3. + 3.50 D. sph. ⊂ + 2.25 D. cyl., axis 75
4. + 3.75 D. sph. ⊂ + 1.75 D. cyl., axis 75
5. + 4.00 D. sph. ⊂ + 1.25 D. cyl., axis 75

The lens combinations tried with the left eye were as follows:

1. — 2.50 D. sph. ⊂ + 3.50 D. cyl., axis 105 (full correction)
2. — 2.25 D. sph. ⊂ + 3.00 D. cyl., axis 105
3. — 2.00 D. sph. ⊂ + 2.50 D. cyl., axis 105
4. — 1.75 D. sph. ⊂ + 2.00 D. cyl., axis 105 (preferred)
5. — 1.50 D. sph. ⊂ + 1.50 D. cyl., axis 105
6. — 1.25 D. sph. ⊂ + 1.00 D. cyl., axis 105

The prescription preferred was:

Right eye: + 1.50 D. sph., axis 90
Left eye: — 1.75 D. sph. ⊂ + 2.00 D. cyl., axis 105

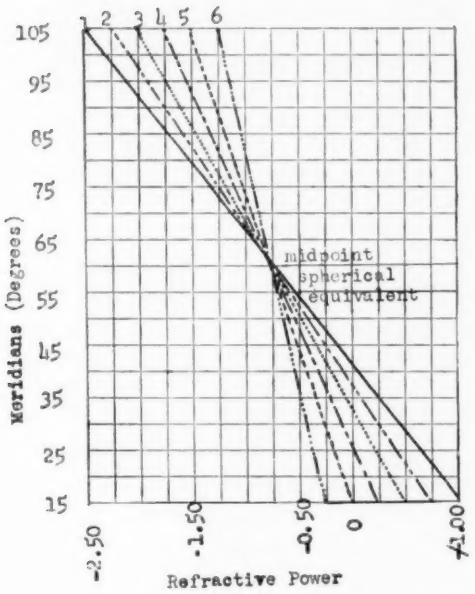

Chart 4.—Schematic representation of lens combinations with the same spherical equivalents as that used in case 4. Combination 4 was preferred.

1. — 2.50 D. sph. ⌒ + 3.50 D. cyl., axis 105 (full correction)
2. — 2.25 D. sph. ⌒ + 3.00 D. cyl., axis 105
3. — 2.00 D. sph. ⌒ + 2.50 D. cyl., axis 105
4. — 1.75 D. sph. ⌒ + 2.00 D. cyl., axis 105
5. — 1.50 D. sph. ⌒ + 1.50 D. cyl., axis 105
6. — 1.25 D. sph. ⌒ + 1.00 D. cyl., axis 105

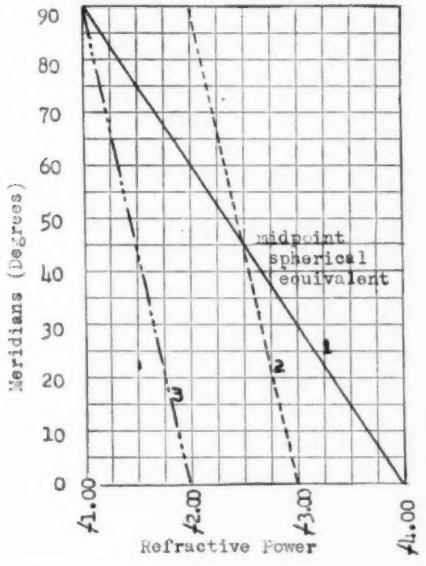

Chart 5.—Schematic representation of the spherical equivalent as compared with the simple reduction of cylinder for a patient with full correction. The full correction, + 1.00 D. sph. ⌒ + 3.00 D. cyl., axis 90, is indicated by line *1;* the spherical equivalent, + 2.00 D. sph. ⌒ + 1.00 D. cyl., axis 90 (reduction of cylinder with proportionate increase of sphere), by line *2*, and the simple reduction of cylinder without change in the sphere, + 1.00 D. sph. ⌒ + 1.00 D. cyl., axis 90, by line *3*.

The value of the cross cylinder in determination of cylinder strength depends on the fact that it does not interfere with the "spherical equivalent" value but changes the sphere and the cylinder in the correct proportions. When a simple cylinder is added to any lens system, however, the optical midpoint is changed, and the "spherical equivalent" value is altered, as shown in chart 5.

CONCLUSIONS

Because of changes in the axis of astigmatism under various monocular and binocular conditions, the final prescription for correction of lenses should be based on testing under binocular fixation. The use of the cross cylinder is advocated as a simple method for such testing. The principle of "spherical equivalents" should be considered in binocular refraction, especially manifest refraction, and in determination of a comfortable binocular prescription in cases of anisometropia.

Mr. J. C. Copeland, of Riggs Optical Company, introduced the principle of spherical equivalents to the residents at the Illinois Eye and Ear Infirmary, Chicago.

A PROBLEM OF SPLIT MACULA

STUDY OF THE VISUAL FIELDS

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AND
JEFFERSON BROWDER, M.D.
BROOKLYN

The course and function of various fasciculi of the optic pathway have held the interest of ophthalmologists and neuroanatomists for many generations because knowledge in this field has a broad application to the diagnosis and treatment of ocular and cerebral disease. There are two general avenues of approach for studies of these fiber bundles. One may produce experimental lesions in various laboratory animals and study the resulting progress of fiber degeneration, or one may make functional studies on human beings who are suffering from certain localized lesions. The difficulties in making functional studies on the visual apparatus of even the subhuman primates are such that one cannot relate degenerative lesions to specific functional defects. For instance, accurate studies of visual acuity and visual fields are necessary to identify the defects caused by the damage to a particular group of fibers. It is recognized that such studies cannot be made on laboratory animals.

Functional studies made on human subjects can be supported by anatomic evidence only when the injury or disease is observed at autopsy or operation. Such primary damage must be so restricted and so located as to exclude secondary involvement of adjacent structures which might give rise to disturbances confusing the picture of the primary lesion. Seldom, if ever, is there opportunity to observe the effects of focal lesions which have been produced under ideal conditions. During World War I minute fragments of missiles on occasion penetrated the brains of soldiers and produced restricted lesions of the cortex and the fiber pathways. The resulting clinical signs were investigated by workers in various warring countries. Their studies arrived at closely similar conclusions.[1] It is obvious, however, that these war injuries may have been complicated by infection, hemorrhage or other damage sustained at the same time. Such material is acceptable only because similar studies by many independent workers supplied data which, when interpreted, forced the same conclusions.

When the presented case of craniopharyngioma afforded an opportunity for special study, it was realized that any evidence derived could be accepted only as part of a general pattern. Investigation of this case seemed especially worth while since no similar studies are recorded in the literature. A review of the literature disclosed but 2 instances in which the optic chiasm was split anteroposteriorly. In 1930 Cushing[2] referred to 2 such cases in his classic paper on the chiasmal syndrome. Haden[3] apparently reported the latter of these cases (that of Miss

Read at the Seventy-Ninth Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 11, 1943.

1. Horrax, G.: Contributions of the War to the Physiology of the Nervous System, Physiol. Rev. **1**:269, 1921.

2. Cushing, H.: The Chiasmal Syndrome, Arch. Ophth. **3**:505 (May); 704 (June) 1930.

3. Haden, H. C.: Studies of the Changes in the Optic Discs, Visual Fields, and Vision Following Bisection of the Optic Chiasm, Tr. Am. Ophth. Soc. **34**:208, 1936.

Betty E.) again in 1936. He had originally referred the patient to Cushing in 1929. Unfortunately, the postoperative studies of the central visual fields in these reports do not supply sufficiently detailed data for comparison with the case here presented. The amount of postoperative vision in Cushing's first case was not actually stated, but the patient was apparently able to read. The best vision in the second, or the Haden-Cushing, case was 6/30 in the right eye and 6/7 to 6/6 (questionable) in the left eye. No reference is made to the correcting glass in either report. It will become evident that these reports are not useful for comparison with data in the present study.

STATEMENT OF THE SURGICAL PROBLEM

The major therapeutic problem that presents itself in an attempted removal of a craniopharyngioma is minimal injury to the hypothalamic nuclei and their connecting pathways. Toward this end three methods of surgical approach were utilized: first, removal of the tumor piecemeal, the optic apparatus being left intact; second, section of the one optic nerve in order to obtain a better exposure of that part of the tumor situated beneath the chiasm, and, third, splitting of the optic chiasm and division of the anterior communicating artery. In the case herein recorded the third procedure was followed.

REPORT OF A CASE

History.—W. M., a 13 year old schoolboy, was admitted in a stuporous state to the Brooklyn Hospital on April 15, 1939. The following notations from the history are pertinent. The middle of 1938 marked the onset of vague headaches, and on rare occasions these attacks were associated with vomiting. During the early part of 1939 the child's interest in schoolwork slackened somewhat. The attacks of headache and vomiting became more frequent, and there was progressive, slight loss of weight. On April 4, 1939, while he was swimming, he asked his brother-in-law to help him from the pool, and immediately the extremities became stiff and the fingers were clenched over the thumbs. The attack was of short duration, and immediate recovery was sufficiently complete for him to dress and go home by subway. On his arriving home there were vomiting and headache, both of which continued at irregular intervals for the next ten days. Also, during this period, there were occasional transitory attacks of generalized rigidity with loss of consciousness. On April 14, the day before his admission to the hospital, the attacks of rigidity became so frequent that he scarcely recovered from one before another occurred. Finally, a continuous state of stupor supervened, accompanied by periodic spells of transitory rigidity and apnea.

Examination.—On his entry to the hospital, examination disclosed flaccid extremities. However, every fifteen or twenty minutes a decerebrate type of convulsion occurred, lasting from one to two minutes, during which all the extremities were held in extension. The face was pale; the lips were cyanotic, and the skin over the trunk was dusky and mottled. The extremities showed a pronounced bluish red mottling; they were cold, and the nails were cyanotic. The pulsations of the peripheral arteries were not palpable. The blood pressure was not obtainable in either the arm or the thigh. The heart rate was 160 per minute. The temperature was 99.8 F. by rectum. After the application of painful stimuli, the patient would rouse sufficiently to push the examiner's hand away and mumble a few unintelligible words. The body contour was characteristic of the Fröhlich syndrome. The pupils were small and did not react to light. Papilledema was present, the elevation being 2 D. in the right eye and 1 D. in the left eye. Paresis of supranuclear origin was demonstrable on the right side of the face. The deep reflexes were not obtained. The abdominal and cremasteric reflexes were present bilaterally but were readily exhausted. The Babinski sign was demonstrable on both sides. Pinprick over all parts of the body evoked facial grimaces and withdrawal of the part stimulated. The red blood cells numbered 7,750,000 and the white blood cells 39,400, with 95 per cent polymorphonuclear leukocytes.

Operation.—It was decided to perform a ventriculographic examination, followed by ventricular drainage by means of a catheter introduced into one of the lateral ventricles. Two hours after admission bilateral postparietal cranial burr holes were made, and the ventricular fluid was completely replaced with air. Roentgenograms disclosed pronounced dilatation of

both lateral ventricles, absence of air in the third and fourth ventricles and a calcific deposit in the suprasellar region, with distortion of the bony outline of the sella turcica. After ventricular drainage there was some improvement in that the patient obeyed simple commands and spoke spontaneously, although somewhat facetiously. The cutaneous cyanosis, the tachycardia (rate 160 to 210 per minute) and the absence of a recordable blood pressure persisted. During the ensuing four days his condition was sufficiently improved to permit further operative measures. On April 19, with use of local anesthesia, a small right frontal bone flap was outlined and turned; the lateral ventricle was tapped, and the chiasmal area was easily identified by elevation of the frontal lobe. A suprasellar cyst was exposed, widely opened and irrigated. The operator not being satisfied that this procedure had relieved the obstruction of the cerebrospinal fluid pathways, the anterior part of the right lateral ventricle was entered, and a blue-domed cystic structure was visualized through an enlarged foramen of Monro. It was determined that this represented the posterior aspect of the aforementioned cyst. The wound was closed, and a transfusion of 300 cc. of citrated blood was administered. The systolic blood pressure was now recorded as 70 mm. of mercury.

Postoperative Course.—Improvement was prompt in every respect, and within three days after the operation the patient was interested in his surroundings and talked intelligently. The peripheral mottling and cyanosis slowly disappeared, and the systolic blood pressure was maintained at 80 to 90 mm. of mercury. No abnormalities of water metabolism were demonstrable. Attempted perimetric examination, on May 6, was not satisfactory, although one could conclude with fair certainty that vision in the temporal fields for 5 mm. white test objects at 330 mm. was not impaired. The patient was discharged from the hospital on May 10. Examination six months later disclosed slight pallor of the optic nerve heads, no defects in the visual fields, a gain in weight of 23 pounds (10.4 Kg.) and normal cellular constituents of the peripheral blood. He returned to school and did well in his studies until about the middle of January 1940. At this time the appetite became poor, and he began to lose weight. During February 1940 he was inattentive in school, complained of headaches and occasionlly vomited. He exhibited irritability, restlessness and periods of listlessness, until his second admission to the hospital, on March 2, 1940. The body contour showed no appreciable change. The optic nerve heads were pale but well outlined. No defect of the visual fields for white was detected. The cytologic constituents of the blood were normal.

Second Operation.—In view of the technical difficulties encountered in previous cases in which complete removal of a craniopharyngioma was attempted, it was planned to expose the cyst by splitting the optic chiasm and dividing the anterior communicating artery. On March 7, 1940 the right frontal bone flap was reelevated and the tumor exposed. The chiasm and the anterior communicating artery were observed to be stretched across the anterior aspect of a cyst. The artery was divided, and without any additional tension being placed on the optic pathways, the chiasm was cleanly divided in the midline with a scalpel. Thereon the tumor was dissected from the circle of Willis and the partially destroyed hypothalamus. The optic tracts were not adherent to the cyst.

Second Postoperative Course.—The postoperative course was characterized by striking arterial hypotension, tachycardia, peripheral cyanosis and a state of what seemed to be peaceful sleep, which persisted for three days. At no time was there a tendency toward hyperthermia. There was a moderate degree of diabetes insipidus, the specific gravity of the urine ranging from 1.004 to 1.009 and the output between 2,000 and 3,100 cc. per day. By the fourth postoperative day the patient was alert and in fair contact with his surroundings.

Pathologic Report.—The pathologist's report on the tissue removed follows:

"The slides represented cross sections of the lining of a cyst. An epithelial layer was present focally and varied from the stratified squamous to the columnar type. Dipping in from the lining layer and scattered through the deeper tissues were islands of epithelium, chiefly of a basal type and containing small cystic spaces filled with secretion, the staining reactions of which varied from blue to purple or pink.

"The epithelial islands were evidently adamantinomatous foci with enameloblastic activity. They were so widely scattered through the excised tissue that it seemed likely that not all of the growth had been excised. The bulk of the tissue consisted of gliotic brain tissue.

"The diagnosis was that of cyst of Rathke's pouch (adamantinoma)."

Further Course.—There was progressive improvement in every respect until the early part of August 1940. At that time the legs and feet became moderately swollen, and the patient complained of recurrent cramplike pains in the lower extremities. He was readmitted to the hospital for study on Sept. 9, 1940. The visual fields at this time showed classic bitemporal

hemianopsia. The fluid intake and urinary output had decreased. The studies did not disclose the genesis of the edema. This slowly subsided, however, and he returned to school.

Progress was satisfactory until the fall of 1941, when, again, inattentiveness, drowsiness and eventually stupor appeared. The terminal picture was, without doubt, the result of a recurrent growth. Death occurred on Nov. 19, 1941. Permission for postmortem study was not obtained.

It was eleven months after section of the chiasm in the midline that the abnormalities referable to the visual apparatus were studied in detail.

STUDY OF OPHTHALMIC ALTERATIONS

From a review of the neurosurgical picture in this case, it is evident that the ophthalmologic interest depends basically on the midline section of the optic chiasm. A most important consequence of the operative procedure was the visual defect. Studies of the ophthalmic evidence, with special emphasis on the defects in the visual fields, were indicated.

From the evidence recorded in the statement of the surgical problem, it seemed reasonably well established that there was no noticeable reduction of visual acuity and no material defect of the visual field prior to the second phase of surgical intervention. On the occasion of the second operation, every effort was made to avoid unnecessary trauma to the chiasm. The incision which divided that structure in the midline was accomplished with precision. On recovery, the visual field showed classic bitemporal hemianopsia.

It seemed reasonable to assume that the progress of the tumor had of itself not accounted for the field defect, but it was equally obvious that the operative procedure and the healing process might have modified the appearance of the visual field and the degree of visual acuity.

It remained, then, to study the visual fields in detail in order to establish their precise characteristics.[4]

Significant Ophthalmologic Observations.—Other than the aforementioned features, no significant points were disclosed by the general or the ophthalmologic history. The patient had never worn glasses, had had no previous ophthalmologic examination and gave no history of ocular injury or disease. Visual acuity in the right eye at the time the first detailed studies of the visual fields were made (July 10, 1941) was 6/21 (0.3) without correction; in the left eye it was 6/12 (0.5) without correction and 6/12 + 3 (0.5 + 3) with a correction of + 1.50 D. sph., axis 180. There was mild convergence insufficiency; no significant anomaly of accommodation or of pupillary response was noted. Study of the fundus in the usual light showed nothing significant except the uniform primary atrophy of the optic nerve. With a red-free light (Friedenwald ophthalmoscope and a yellow-green filter) the nasal portion of the retina of each eye had a woolly appearance. The temporal portion of the retina gave the characteristic reflex of the nerve fiber layer. No peculiarity of the macula or the paramacular region was disclosed, nor were any changes in the nerve heads apparent with "restricted light." Neither slit lamp

4. It is necessary that we emphasize our attitude toward "relative defects." A relative defect is plotted in response to the subject's description of qualitative variations in the brightness of the (stimulating) object. Hence the scotoma can be no more than a qualitative indication, which may be quite different in size and shape at a subsequent examination, owing to the patient's selection of different descriptive language and standards of brightness. Any reliable defect can be, with appropriate technic, converted into an absolute defect. Under these conditions, the subject merely reports on the presence or absence of the stimulus. The plotted scotoma is measurable, and the conditions of study are reproducible and are less subject to the psychologic whims of the patient. One of us has emphasized elsewhere the clinical unreliability of color fields.[7]

nor other standard methods of study elicited significant evidence. No studies were made of light sense, color sense or perception of movements in the visual fields.

Visual Fields.—As seen in figure 1 *A* and *B*, the field as plotted by means of the perimeter seemed to indicate that the macula had been spared by about 10 degrees. The perimeter, however, is not adapted to precise study of the central fields although projection perimetry was used in this instance, as described elsewhere.[5] Hence a second study (fig. 1 *C*) was made of the fixation region by use of the stereocampimeter and an object 0.4 mm. in diameter.[6] Tests with this object have been shown to give reliable results when fixation is normal.[7] Even with this technic, fixation was not assumed to be perfect, since the corrected visual acuity was not (20/20) 6/6 (1). This led to the conclusion that a central scotoma must be present; so a third study (fig. 1 *D*) was made, the stereocampimeter and a 0.2 mm. object being used. Considerable past experience had shown that

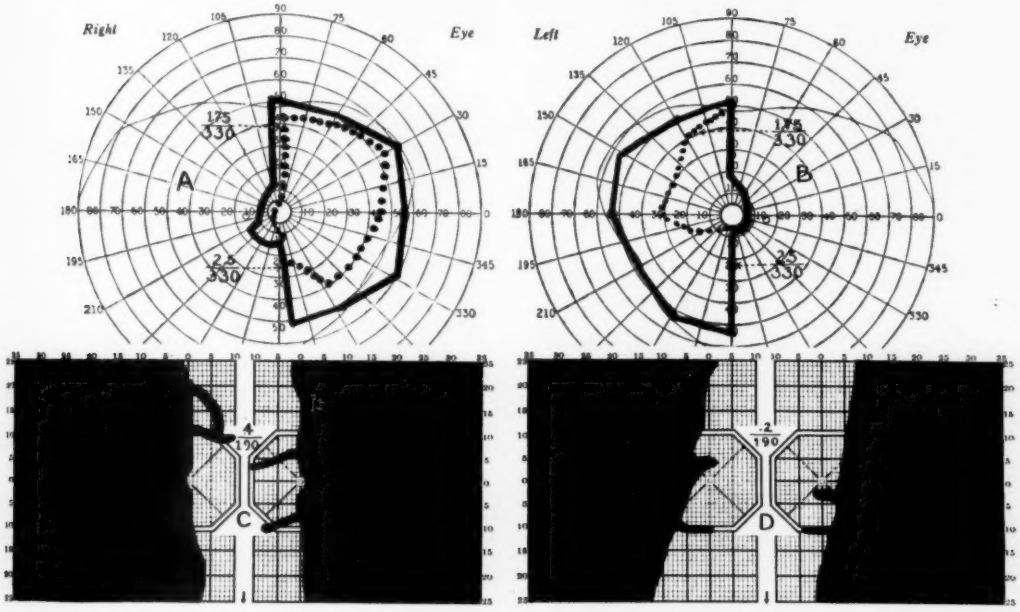

Fig. 1.—Results of surgical anteroposterior division of the chiasm in the case of a 13 year old boy with a craniopharyngioma (tumor of Rathke's pouch). Vision was 6/15 + 3 with correction in the right eye and 6/12 + 3 with correction in the left eye.

A and *B* are perimetric fields, and *C* and *D*, stereocampimetric charts taken with 0.4 and 0.2 mm. objects respectively.

this technic[8] could be depended on to demonstrate a central scotoma even when visual acuity had dropped from (20/20) 6/6 to (20/16) 6/4 so that it seemed likely that it would reliably demonstrate a scotoma capable of reducing 6/6 vision to (20/40) 6/12.

5. Evans, J. N.: The Perimeter Spot-Light Object, Arch. Ophth. **7**:614 (April) 1932.

6. White letters on a black background under 10 foot candles of illumination were used as the test object. These letters were checked for accuracy of size.

7. Evans, J. N.: An Introduction to Clinical Scotometry, Cambridge, Mass., Yale University Press, 1938, pp. 29-43.

8. Though the stereocampimeter was employed, it was used as a monocular device, the affected eye fixing the imaginary center of a drawn circle. A white spherical object was used against a black background at a distance of 190 mm. under 15 foot candles of illumination.

These expectations were fulfilled (fig. 1 *D*) by the demonstration of a finger-like absolute central scotoma which appeared protruding from the blind field above the point fixed. One must realize that the central scotoma could not cover the point fixed, since, macular function being impaired, the paramacular retina was used for this purpose. The true position of the macula was necessarily represented by some point within the finger-like scotoma.

From previous studies on a number of patients with strabismus who were subject to central scotoma [9] and from unpublished studies with the ophthalmograph [10] on fixation movements in such subjects and on normal subjects with after-image central scotomas (fig. 2), it was evident that nystagmoid movements must have modified fixation in the present case.[11]

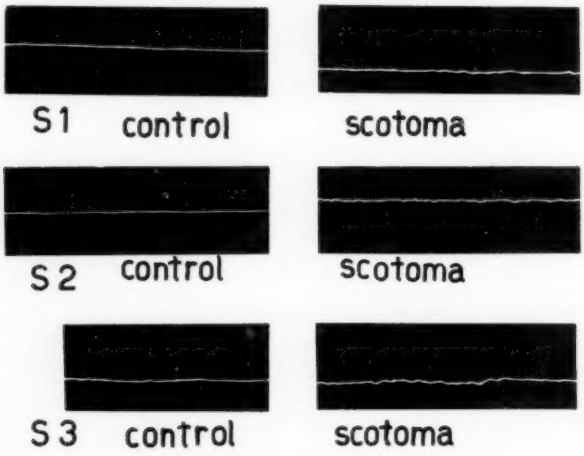

Fig. 2.—Tracing of ocular movements during fixation at 1 meter in a normal subject with after-image central scotoma.

Fig. 3.—Ophthalmographic records of fixation movements. In each instance the subject fixed on a campimeter background (the fixation point being a chalk mark) at 190 mm. through a + 5.25 spherical lens, the conditions of mononuclear fixation as employed during campimetric examination being thus duplicated. A 0.4 mm. object was employed to map in the region of the fixation point.

A indicates the fixation movements of the patient (W. M.), whose chiasm had been divided anteroposteriorly at operation. *B* indicates the fixation movements of a patient who had no known pathologic disturbance of the visual fields or of ocular movements.

9. Evans, J. N.: Scotoma Associated with Strabismus, Am. J. Ophth. **12**:194 (March) 1929.

10. To all intents and purposes this device is a camera which takes a continuous photograph of the corneal reflex on a moving picture film, which is in continuous motion. The result is a white tracing which represents fixation movements in the horizontal plane.

11. We have long been of the opinion that other workers have not given sufficient consideration to fixation movements when reporting on the shape and size of minute central defects.

In order to comprehend the significance of these movements, the last plotting (fig. 1) was repeated under identical conditions, but with the subject seated before the ophthalmograph. The ophthalmographic reading (fig. 3 *A*), which is presented with a similar tracing for a normal subject (fig. 3 *B*), indicates the expected instability of fixation in the horizontal meridian. It is noted that the so-called normal nystagmoid movements are recorded by the ophthalmograph as an almost unwavering straight line, whereas the tracing for the patient shows many steplike breaks. A great number of these steps were measured from a midline. The average deviation to each side of this midline was 0.89 mm.[12]

It thus seemed evident that these fixation movements modified the size and shape of the scotoma. In order to evaluate this effect, we thought it desirable to determine the actual magnitude of the ophthalmographic variations. To that end a separate study was made, normal subjects being used. The results indicated that the nystagmoid movements covered about 3.75 mm. on the campimetric chart, the horizontal diameter of the scotoma being thereby lengthened by 3.75 mm.

Study of Nystagmoid Movements of Normal Eyes.—With the aid of the ophthalmograph, studies were made on normal eyes to determine the fixation movements that occurred while the subjects were attempting to maintain constant fixation during the plotting of the central visual field. The experiments were so arranged as to duplicate, as nearly as possible, fixation relations as they pertained to clinical studies with the tangent screen and the campimeter at 2 meters, 1 meter, 33 mm. and 190 mm. Repeated attempts to make direct studies in this way demonstrated that the ophthalmograph is not sufficiently sensitive for this purpose. McFarland, Holway and Hurvich[13] apparently arrived at a similar conclusion with regard to the value of the standard ophthalmograph for this purpose.

Another method was therefore employed in order to interpret the deviations of the ophthalmographic record. Experiments on normal subjects were first performed in which fixation was moved successively over five 1 degree jumps and then back to the original fixation point in one 5 degree jump. This was accomplished by having the subject fix, in succession, the center of the 1 degree squares of the stereocampimetric chart. The ophthalmologic record was later projected on a screen for study. By this means it was concluded that a deviation on the ophthalmographic record of 0.71 mm. corresponded to a shift in fixation of 1 degree of the normal eye.

As previously stated (page 48), the fixation movements in the case under study averaged 0.89 mm. on the opthalmographic film during the mapping of the scotoma. It thus seems obvious that the fixation movements in this case covered about 1.25 degrees in the horizontal meridian. Each campimeter square was equivalent to 1 degree and measured 3 mm. in diameter. Thus a deviation of 1.25 degrees in this case was equivalent to 3.75 mm. on the campimeter.

It was recognized that duration of fixation influences the amplitude of oscillations, so that every effort was made to shorten the period during which the patient had to maintain fixation.

Scotometric Studies.—The exact horizontal limits of the scotoma could not be measured because one end merged with the half-field defect.

12. For convenience, the photographs of these records are placed horizontally in the illustrations; hence horizontal movements of the eyes are shown as vertical steps.

13. McFarland, R. A.; Holway, A. H., and Hurvich, L. M.: Studies of Visual Fatigue, Cambridge, Mass., Harvard University Press, 1942, p. 137.

The length of the scotoma (average values from a number of studies), measured at a level equidistant from the upper and the lower border and extending from its base at the edge of the area of hemianopsia to the tip of the scotoma, was 16 mm. As already stated, the error due to fixation movements would seem to be not greater than 3.75 mm. This is to be subtracted from the plotted length of the scotoma. The horizontal diameter of the scotoma would thus appear to be 12.25 mm. on the tangent surface of the campimeter placed at 190 mm. from the subject's eye (fig. 4).

No graph to show vertical fixation movements was obtained, but such movements must have been minute because the horizontal angioscotoma mapped on each chart as a control of accuracy showed no width greater than one finds in normal subjects. The average width of the angioscotoma of the vessels arching over the macula, determined by measurements of 100 maps carefully selected and controlled to insure reliability, was 4.1 mm., measured on a line bisecting the fixation point (fig. 1 *C* and *D*). Hence it is probable that the horizontal and the vertical diameter of this scotoma were respectively 12.25 and 7.2 mm., or about

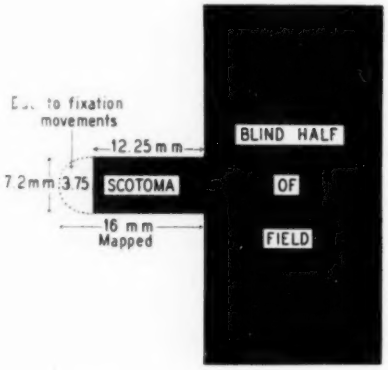

Fig. 4.—Diagram of the scotoma of the macula associated with a defect of the crossed fibers.

4 and 2.5 degrees. This, then, was the size of the scotoma resulting from division of the chiasm in the midline (fig. 4).

It is to be noted that the chart does not show the classic shape of the central scotoma hemianopsia. It is recognized that the shape and size of the scotoma may have been modified by an abnormal angioscotoma, but pressure on the globe did not change the size and shape of this finger-like projection (fig. 1) beyond 9 degrees from its base.[14] In this particular study, the scotoma seemed to have a horizontally oval form. Though some authors have plotted central scotomas which were identical in shape with those associated with hemianopsia, we do not feel that the technic was sufficiently controlled to warrant our acceptance of their results.

If the concept that the macular fibers[15] form a semidecussation in the chiasm is adopted, then in the case cited the surgical procedure divided all the crossed

14. It has been demonstrated elsewhere[7] that a normal angioscotoma extends horizontally 7 to 8 degrees from the blindspot. This region widened only with pressure on the globe in the present study. The remainder of the defect would thus seem to be due to damage to fiber bundles.

15. For the sake of a clearer mental picture, all consideration of the extramacular fibers of the pathway is omitted.

macular fibers, with the result that the corresponding part of each macula was rendered functionless. This scotoma, then, may be assumed to represent the approximate size and shape of the part of the macula supplied by the crossed fibers (fig. 5).

Since macular function is commonly measured by determination of visual acuity, one is led to inquire what the visual acuity of the intact half-macula should be. A study of this case should supply the answer. Numerous efforts have been made to study the visual acuity of the eccentric retina, but no one, in our opinion, has presented acceptable evidence for various points within the macula. This is because precise fixation cannot be guaranteed.

From evidence supplied by studies reported elsewhere,[7] it seems that a fixing eye with a small central scotoma will be turned or aimed in such a direction as to use the most highly developed isopter which remains undamaged. In this instance (in which it was temporal) the eye would automatically fix with the seeing half-macula (that part of the retina adjacent to the dividing line of the area of hemianopsia). Thus, if in a given case visual acuity (6/6 being accepted as normal) before the damage occurred was 6/6 and remained 6/6 after the hemianopsia had appeared, one might be justified in saying that macular function had been spared. In such a case, the dividing line between the seeing and the nonseeing half-field might show a notable degree of sparing, or it might seem to divide the fixation point. If, on the other hand, vision was reduced to 6/12 and the dividing line seemed to pass directly through the fixation point, one might contend that the macula had been split, with the temporal half left intact and the nasal half [16] destroyed, or one might contend that the entire macular function had been destroyed and that the 6/12 vision represented the retina adjacent to the macula. But we have accepted semidecussation; hence only half the macula can be left. It will be noted that the visual acuity of our subject was about 6/12.

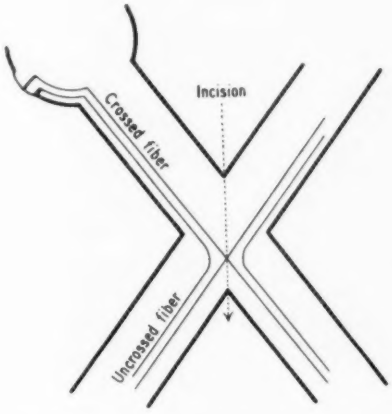

Fig. 5.—Diagram of the macular fibers.

That the dividing line for hemianopsia in this case bends away from the fixation point on the chart (fig. 1), so that the macula is left outside the blind area, is of course not evidence that the macula was spared (fig. 1) unless corrected visual acuity remained normal. It cannot be emphasized too strongly that defective vision not due to a refractive error or to opaque mediums must result

16. The word "half" is used not with the meaning of a mathematically precise portion but in a gross anatomic sense only.

from defect in the visual field in the classic sense. When the visual defect is not explainable by changes in the eyegrounds, it must be referred to damage to visual pathways.

The mere presence of poor vision, then, implies the presence of a scotoma involving fixation, and it must be realized that such a defect cannot coincide with the fixation point as indicated on the plotting chart because that is being fixed by an eccentric portion of the retina not corresponding to the defect. Of course, the subject can displace the central scotomatous area by using the unaffected eye for fixation, but this only obscures the fact that such binocular vision is upset and that the defect is not actually in the plotted position. (The normal eye is fixing with the isopter of 6/6 vision, and the other, with the isopter of 6/12 vision.)

COMMENT

A great many methods have been suggested for maintenance of fixation. The complementary color method of Schlosser, the stereoscopic method of Haitz and the macula selector of Walker were great improvements over earlier ones, but the mere fact that they demand good binocular coordination at a time when one eye is constantly thrown out of line by the scotoma is evidence enough that they cannot secure maintenance of the necessarily refined fixation. Numerous other methods in which the sound eye was supported to steady the eye under study have, of course, been advised. These methods have a justifiable place in the average clinical work, but one gains a false feeling of security because the central scotoma falls so neatly on the fixation point of the chart. A much more perfect check on the accurate positional relation and shape of such a defect is, for instance, the position of the borders of the normal blindspot or of the adjacent angioscotoma. In fact, there is a physiologic effort to line up these mapped normal defects with their tracings on the campimetric chart. The use of these landmarks insures accurate fixation in normal subjects to within 0.25 degree, as concluded from many thousands of studies on angioscotomas; moreover, one can continually check the fixation while plotting the central scotoma. Halstead, Walker and Bucy [17] checked fixation by recording corneoretinal electrical potentials by means of an elaborate, but precise, instrumental setup. This method recorded ocular movements of less than 0.5 degree of arc. (These workers use test objects subtending a visual angle of 15 minutes. It is thus possible that, unknowingly, they may have been plotting angioscotomas—possibly pathologically enlarged or widened by such factors as menstruation and low blood pressure. These same investigators also checked their work, in certain instances, by means of a camera for ocular movements. Their equipment also recorded movements of the head and the subject's responses to disappearance of test objects. They could check both vertical and horizontal ocular movements. Their camera did not seem to be the well known ophthalmograph.)

It thus seems justifiable to assume that the present study, with the technic of angioscotometry, is as accurate and dependable as the more elaborate and less clinically useful methods employed by other workers. One could not conclude, however, that the nystagmoid movements studied arose from the presence of the central scotoma alone, as the surgical traumatism and the pathologic process may have contributed to their production. In fact, it cannot positively be contended that the scotoma was entirely due to the splitting of the chiasm, because other, and

17. Halstead, W.; Walker, A., and Bucy, P.: Sparing and Nonsparing of "Macular" Vision Associated with Occipital Lobectomy in Man, Tr. Sect. Ophth., A. M. A., 1940, p. 193. Their special instrument showed sparing of the macula of 2.5 degrees.

considerable, damage must have occurred from the surgical measures and the action of the tumor and healing process.

Reports of this type are definitely worth while, however, if supported by enough corroborative evidence from studies of a similar type. One other aspect of this subject might receive consideration. In the present case a scotoma due to a lesion of the crossed macular fibers extending into the field of the seeing (temporal) portion of the retina has been noted. If the line between the seeing and the blind half of the retina runs through the fixation point, it is necessary to explain how the blind nasal area of the macula is found in the seeing temporal extramacular field. If the projection of the macula is regarded as a field separate and distinct from the rest of the projected retina, then it can be assumed that the macular field is eccentrically placed in the extramacular field. It is not possible to determine the degree of eccentricity until a study of the field resulting from dysfunction of the uncrossed macular fibers has been made. It seems impossible to make such a study by division of the uncrossed fibers, but perhaps some case may appear in which the field of the intact papillomacular bundle will alone remain undamaged (as in cases of quinine poisoning). It will then be possible to compare the results with the observations in the case here presented and to deduce the character and extent of the defect characteristic of dysfunction of the uncrossed macular fibers. That nasal elements are offset in the temporal area is not a novel idea when it is recalled that the papilla containing temporal fibers is far offset to the nasal side. Reference to figure 5 shows a simple and possible arrangement of fibers which may help to explain this point.

One must also keep in mind possible anatomic variations which might bring the line of crossing of macular fibers to one side of the chiasm, so that final visual acuity would vary from case to case.[18]

It is altogether possible that both crossed and uncrossed macular fibers supply the whole macular area so that the scotoma shown represents only a partially blind, or "depressed," area, a possibility accounting for the offset position of the defect and the reduced visual acuity.

CONCLUSIONS

The results of the present study seem to permit the following conclusions:

The methods we have employed in this study are more adequate than those of other workers.

The visual acuity resulting from division of the crossed macular fibers is approximately (20/40) 6/12 and permits the subject to read and write such material as he is apt to need in average daily life.

The divided macular fibers crossing in the optic chiasm in this case did not give rise to the half-moon scotoma.

Fixation movements require consideration in determination of the size and shape of the defect.

The entire macula must be supplied by both crossed and uncrossed fibers.

These observations should be of assistance to the neurosurgeon and the ophthalmologist, who may have occasion to study similar cases.

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18. In Haden's case vision in the left eye was 6/6. "Electrical" cutting was used to divide the chiasm in this case.

PENICILLIN AND SULFADIAZINE IN THE TREATMENT OF EXPERIMENTAL INTRAOCULAR INFECTIONS WITH STAPHYLOCOCCUS AUREUS AND CLOSTRIDIUM WELCHII

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The study of the chemotherapy of intraocular infections of the anterior segment with Diplococcus pneumoniae [1] was extended in these experiments to similar infections with Staphylococcus aureus, which stands second to D. pneumoniae in frequency as the cause of post-traumatic and postoperative purulent endophthalmitis, and Clostridium welchii was selected as a representative of the anaerobe group. The effect of the oral administration of sulfadiazine in combination with the topical use of its sodium salt was again compared with that of the local treatment with penicillin.[2]

INFECTIONS WITH STAPHYLOCOCCUS AUREUS

Preliminary Experiments.—Eight strains of Staph. aureus, obtained in cultures of material from human conjunctivas and corneas,[3] were tested in vitro for their sensitivity to penicillin. The determinations were made in accordance with the modified method of Fleming [4] except for the use of a 10^{-2} dilution of the broth culture in place of a loopful of the latter per 5 cc. of broth. Two strains of mannitol-positive hemolytic Staph. aureus of average sensitivity to penicillin were used for inoculation of the eyes of mature chinchilla rabbits. Strain W was isolated from the conjunctiva of a patient with severe postoperative endophthalmitis. Strain K was grown from material obtained from a fulminant corneal ulcer of a diabetic patient. The injection of cultures of these strains into the anterior chamber did not lead with certainty to severe destructive endophthalmitis. Such an inflammation was produced, however, when the surface of the lens was deeply incised during the procedure of inoculation. The standard lesion thus obtained was a satisfactory test object for the chemotherapeutic experiments with staphylococci. The histologic changes were studied at various stages of the infection.

TECHNIC

Inoculation.—The pupils were dilated with atropine; moderately deep sleep was induced with pentobarbital sodium, and local anesthesia was effected with a 0.1 per cent solution of nupercaine hydrochloride. The technic described in the experiments with pneumococci was modified to avoid the injection of air after the withdrawal of aqueous and the insertion of the syringe filled with the diluted culture. A small three way stopcock was armed with a 27 gage needle and connected with two tuberculin syringes. The needle was introduced into the anterior chamber near the limbus at 12 o'clock, and a large, deep slit was made in the anterior cortex of the lens. Aqueous was withdrawn into one syringe, and after the proper adjustment of the stopcock, a net amount of 0.05 cc. of a 10^{-4} dilution of an eighteen hour broth culture was injected into the anterior chamber. The number of viable organisms injected, as calculated by plate counts, varied from 5,000 to 10,000. After

This study was supported by the Knapp Memorial Foundation.

From the Department of Ophthalmology of Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital.

1. von Sallmann, L.: Penicillin and Sulfadiazine in the Treatment of Experimental Intraocular Infection with Pneumococcus, Arch. Ophth. **30**:426 (Oct.) 1943.

2. The penicillin was extracted and prepared in the laboratory of Dr. Karl Meyer.

3. Dr. Devorah Locatcher-Khorazo did all the bacteriologic work on the human eye in connection with this experimental study.

4. Fleming, A.: In-Vitro Tests of Penicillin Potency, Lancet **1**:732, 1942.

withdrawal of the needle an attempt was made to seal the puncture canal with a heated probe, but in many instances some fluid leaked out of the wound. The lids were kept closed for several hours by fixing the upper lashes on the cheek with a small strip of cellulose tape.

Treatment.—Treatment was initiated six to seven hours after inoculation and consisted of the iontophoretic introduction of sulfadiazine or of penicillin. The ionization method was selected for local therapy because previous experiments[5] had shown that it greatly increased the concentration of both drugs in the aqueous. In addition, this treatment had been found to be well tolerated by the human eye. Application of sodium sulfadiazine in a 5 per cent solution for five minutes at 2 milliamperes was supplemented by the oral administration of 0.25 Gm. of sulfadiazine per kilogram of body weight each day. Sodium penicillin was used locally in a solution of 0.25 per cent at the same millamperage and for the same length of time as the sulfonamide salt.[6] The local applications were generally repeated twice a day on the two succeeding days (one application of five minutes and one of three minutes) and once a day for the next three days. Treatment was discontinued if the anterior segment became completely suppurative.

RESULTS OF PRELIMINARY EXPERIMENTS

Of the 8 manitol-positive strains of hemolytic Staph. aureus, 5 were isolated from the conjunctiva, 2 from corneal ulcers and 1 from a cystoid scar resulting from an Elliott trephination followed by a severe late infection. Four of the strains were obtained from patients whose eyes had been treated unsuccessfully with sulfonamide drugs for several months in preparation for extraction of cataract. The sensitivity to penicillin of all strains was within the same range; that is, growth in a 10^{-2} broth culture was inhibited by 0.187 to 0.625 microgram per cubic centimeter of a relatively crude preparation of penicillin. The strain with the greatest sensitivity to penicillin (0.187 microgram per cubic centimeter) showed less virulence than other strains on inoculation into the anterior chamber of rabbits.

The conjunctiva and the border of the lid of 2 patients were rendered free of sulfonamide-fast strains of Staph. aureus haemolyticus two and five days respectively after treatment consisting of hourly instillations of a 0.25 per cent solution of sodium penicillin for a daily period of twelve hours. For 2 additional patients the cultures were negative twenty-four hours after initiation of the treatment, but no previous attempt had been made to influence the flora with sulfonamide compounds.

The clinical and histologic inflammatory changes observed six hours after inoculation of the eyes of rabbits were caused in great part by the trauma of the injection. To this category belong the dense fibrinous exudate in front of the pupil, the dilatation of the capillaries in the iris and the ciliary body, the obvious increase in protein content of the aqueous, the presence of a few polymorphonuclear leukocytes in the iris and the anterior chamber and the characteristic edema of the ciliary processes in the form of numerous Greeff blebs. The changes agree well with the signs of inflammation described by Poos[7] as the hypotonic effect of paracentesis in rabbits. The presence of clumps of polymorphonuclear leukocytes in the anterior chamber and the purulent exudate at the pupillary border should be attributed to the infection since these signs were not evident in control eyes with

5. (*a*) von Sallmann, L.: Sulfadiazine Iontophoresis in Pyocyaneus Infection of Rabbit Cornea, Am. J. Ophth. **25**:1292, 1942. (*b*) von Sallmann, L., and Meyer, K.: Penetration of Penicillin into the Eye, Arch. Ophth., this issue, p. 1.

6. A calcium salt of penicillin was prepared by Dr. Karl Meyer for tentative experiments with iontophoresis in a series of 8 eyes. The iontophoretic introduction of a 0.25 per cent solution caused an extensive abrasion of the cornea and fibrinous exudate in the anterior chamber.

7. Poos, F.: Ueber die histologischen und klinischen Erscheinungen bei akuten, lokalen Capillarkreislaufstörungen am Auge, Arch. f. Ophth. **127**:489, 1931.

injections of sterile broth. In many instances the clumps of leukocytes, suspended in the fibrin network in front of the cataractous lens, could be seen macroscopically.

At this stage sections stained by Verhoeff's [8] modification of the Gram-Weigert method revealed numerous organisms on the surface of the exposed lens fibers. No organisms could be detected with certainty in other parts of the anterior chamber. Beginning invasion of the wound in the lens by polymorphonuclear leukocytes was noted.

All signs of inflammation increased greatly in the following eighteen hours. This stage was characterized by a dense infiltration of the limbus and extensive purulent exudate in the anterior chamber, with several layers of leukocytes at the posterior surface of the cornea. The deeper staining of the anterior and the posterior chamber with eosin indicated the high protein content, but frequently only a few leukocytes were present in the posterior chamber and vitreous cavity. The wound in the lens was covered with exudate and masses of leukocytes, which also infiltrated the superficial and the deeper layers of the anterior cortex.

Results of Sulfadiazine and Penicillin Treatment Beginning Six to Seven Hours After Injection of a 10^{-4} Dilution of Staph. Aureus into the Anterior Chamber with Simultaneous Injury of the Lens

Treatment	Strain of Staph. Aureus Injected	Number of Eyes	Number of Eyes		
			Recovered	Temporarily Improved	Lost
Sodium sulfadiazine iontophoresis and oral use of sulfadiazine	W	11	4	—	7
	K	12	1	—	11
Control eyes (influenced only by oral use of sulfadiazine	W	5	1	—	4
	K	8	—	—	8
Sodium penicillin iontophoresis	W	12	6	3	3
	K	12	9	—	3
Control eyes (no treatment)	W	10	—	—	10
	K	9	—	—	9

In the later stages the purulent endophthalmitis spread into the posterior chamber and the vitreous, soon involved the nerve head, destroyed the retina and finally the choroid and so led to the histologic picture of panophthalmitis.

RESULTS OF TREATMENT

The course of the experimental endophthalmitis and the results of the treatment indicated that strain K had a higher animal pathogenicity than strain W and that infections with the first strain were more difficult to control by either type of chemotherapy (table).

Five out of 23 eyes were saved by the combined oral and topical use of sulfadiazine. The other 18 eyes were destroyed by the infection. The condition in 1 of 12 eyes infected with strain K was cured by therapy with the sulfonamide compound.

Fifteen out of 24 eyes were successfully treated by the local use of sodium penicillin. In 6 eyes the inflammation progressed from the beginning in spite of

8. Verhoeff, F. H.: Observations on Parinaud's Conjunctivitis (Leptothricosis Conjunctivae), Am. J. Ophth. **1**:706, 1918.

the therapy. The other 3 eyes were considered healed after treatment for three days, but the inflammation flared up about a week later. It could not be checked by renewed treatment with penicillin. The therapy was continued a few days longer in the succeeding series, and thereafter no relapses occurred. Nine out of 12 eyes infected with strain K responded well. In 1 rabbit one eye was treated with sodium penicillin and the other with sodium sulfadiazine; in addition sulfadiazine was given orally in the usual dose. The eye treated locally with the sulfonamide compound suppurated; the infection in the penicillin-treated eye was checked.

In all 19 untreated control eyes of the penicillin series destructive purulent endophthalmitis developed. The infection cleared up in 1 of the 13 control eyes of the sulfadiazine series which were influenced by the daily oral administration of 0.25 Gm. of sulfadiazine per kilogram of body weight.

Penicillin therapy produced three times the number of good results as did the combined sulfadiazine treatment (62.5 to 21.7 per cent). This contrast would presumably have been even more striking (75 to 21.7 per cent) if the period of treatment with penicillin had been extended a few days longer in the first group of experiments.

COMMENT

Thygeson,[9] in his review of the treatment of ocular infections with sulfonamide compounds, stated that staphylococci are relatively resistant to these substances. He found, however, that topical applications were of value for external infections with this organism, such as blepharitis, conjunctivitis and corneal ulcer. He also reported 7 cases of intraocular infection with staphylococci, in 4 of which the condition responded satisfactorily to treatment with a sulfonamide compound, in 2 slowly and in 1 not at all. In 5 of 7 cases of staphylococcic panophthalmitis previously listed by Guyton and Woods[10] treatment with sulfonamide compounds was successful. In the absence of operation, the certainty of the etiologic diagnosis in cases of endophthalmitis and panophthalmitis not of metastatic origin is weakened, however, by the recognized difficulties of the bacteriologic examination.

The experimental work on modern chemotherapy of staphylococcic infections of the eye has been confined to corneal inoculations. No conclusions can be drawn from the single observations of Meoni,[11] but the extensive study of Robson and Scott[12] is informative in its comparison of the effects of various chemotherapeutic agents on a fairly well standardized corneal lesion. Penicillin was found more beneficial than sulfacetimide, and also more effective in prevention. The use of "solubilized" sulfathiazole[13] gave disappointing results, and tyrothricin[14] was of only slight benefit. To my knowledge no experimental data on the results of chemotherapy of intraocular infections with staphylococci are on record.

The reliability of the standardized intraocular lesion reported in the present paper is open to criticism. To the general inaccuracies of biologic experiments must be added the following possibilities of error inherent in the technic: The unavoidable escape of an uncontrolled amount of the injected broth culture resulted

9. Thygeson, P.: Sulfonamide Compounds in Treatment of Ocular Infections, Arch. Ophth. **29**:1000 (June) 1943.

10. Guyton, J. S., and Woods, A. C.: Use of Sulfanilamide in Ophthalmology, Am. J. Ophth. **24**:428, 1941.

11. Meoni, M.: La chemioterapia sulfamidica nelle affezioni oculari, Arch. di ottal. **46**: 183, 1939.

12. Robson, J. M., and Scott, G. I.: Local Chemotherapy in Experimental Lesions of the Eye Produced by Staphylococcus Aureus, Lancet **1**:100, 1943.

13. "Solubilized" Sulfathiazole is a 15 per cent solution of sulfathiazole sodium formaldehyde sulfoxylate.[12]

14. Tyrothricin consists of 15 per cent gramicidin and 85 per cent tyrocidin.

in variations in the size of the inoculum. The depth and extent of the opening in the lens and the intensity of the trauma were also not constant. The course of the control lesion was sometimes fulminant and sometimes subacute. To compensate for the differences in the initial lesions, however, the eyes with more pronounced inflammatory reactions as observed with the slit lamp were selected for local treatment, and those with minor signs of infection were used as controls.

The contrast between the efficacy of sulfadiazine and that of penicillin noted in treatment of experimental intraocular infections with pneumococci was not as striking in experiments with staphylococci. It was evident, however, that the topical application of penicillin definitely checked infections with two strains of Staph. aureus much more frequently than did combined sulfadiazine therapy. The results in the sulfadiazine series illustrate, again, the importance of supplementation of systemic therapy with local treatment. The topical application of penicillin shows the effect of comparatively high levels in the aqueous exerted for several hours. It is probable that the number of good results can be increased by combining iontophoresis with a method which will produce a moderate but sustained level of penicillin in the aqueous. Previous attempts to obtain this condition by the repeated use of ointments or instillations, including the combination with wetting agents, did not result in any noticeable antibacterial activity of the aqueous.[5b] No attempts were made to introduce penicillin systemically, for reasons cited in the same paper.

Florey and Florey [15] emphasized that a bacteriostatic concentration of penicillin must be maintained at every point at which there are infecting organisms. Desirable as this aim may be, it is difficult to attain in the various structures of the eye. A continuous bacteriostatic concentration may be obtained in the aqueous with improved therapeutic methods, but in the lens or vitreous it can hardly be achieved without an extreme and sustained rise of the level of the drug in the aqueous or the blood. It is of interest, therefore, that a large number of infections of the lens were checked by a method which produced only a transient high concentration of the antibiotic agent in the aqueous. The high levels obtained by iontophoresis are not essential, however, in treatment of infections of the anterior chamber without injury to the lens, as the use of the corneal bath in cases of pneumococcic infection showed.[1] In general it may be assumed that with acute, virulent infections with organisms of moderate sensitivity to penicillin, especially those involving the lens, higher concentrations are desirable.

The humoral and cellular body defenses, although unable to overcome the experimental infection of the lens, are certainly of importance in the final outcome. In view of the results, there is no reason to assume that iontophoresis interferes with body defenses, or if such interference does occur, it is compensated for by the beneficial effect of the chemotherapeutic compounds. Further studies are necessary to clarify various aspects of this problem.

The question of corneal damage by the treatment was discussed in a previous paper.[1] Since then iontophoretic applications with penicillin have been used in a series of patients, and no undue effects, especially no abrasions, have been noted.[16] In rabbits, abrasions occurring after repeated applications on the same

15. Florey, M. E., and Florey, H. W.: General and Local Administration of Penicillin, Lancet **1**:387, 1943.

16. An applicator tube, similar to that of van Heuven, and made of lucite by Obrig Laboratories, New York, was found useful for clinical purposes. One end of the tube has a broad flare, in the form of the scleral part of a contact lens. The diameter of the opening is approximately that of the cornea. Five millimeters above this aperture a spiral of platinum wire is contained in a widening of the tube. An extension of the wire provides a connection to the lead of the apparatus for iontophoresis.

day generally heal quickly, but in 2 animals (1 in the pneumococcus series and 1 in the staphylococcus series) a large abrasion was followed by a strong inflammatory reaction, leading to a central scar. These experimental results are in agreement with Bellows'[17] observation that "topical application of [sulfonamide compounds] to the denuded cornea retards epithelial regeneration and promotes scarring." Corneal lesions can be avoided, however, even in the more sensitive cornea of the rabbit, by proper timing of the treatment and adequate dosage.

The importance of continuation of penicillin therapy for a few days after the inflammation appears to be checked macroscopically was mentioned in experiments with pneumococci. Florey and Florey[15] also stressed the indication for continued treatment after an apparent cure. These statements were confirmed by the occurrence of relapses in 3 cases of staphylococcic infection in which iontophoretic applications were discontinued too soon.

In experimental infections of the cornea with staphylococci the value of sulfonamide compounds and of penicillin lies, according to Robson and Scott,[12] in the prevention of acute infections rather than in their treatment, as these authors obtained good results only when chemotherapy was begun one hour after inoculation. Observations on intraocular infections treated with penicillin do not support their opinion. Penicillin was effective in many eyes with an initially violent inflammation. This was especially noticeable in the gradual improvement of pneumococcic infections with a twelve hour interval between inoculation and treatment. The definite therapeutic activity of penicillin was further indicated by its control of 3 cases of progressive pneumococcic endophthalmitis resistant to sulfadiazine therapy.[1] No beneficial effect was evident in eyes in which the acute endophthalmitis had reached a climax. The six hour interval between the infection and the first treatment was not extended in experiments with injury to the lens because the more violent infections pursued an acute course and reached a climax within twelve hours.

The experimental results of treatment with sulfadiazine and penicillin were obtained on infections with two strains of staphylococci. The eight strains tested in vitro varied slightly in their susceptibility to penicillin. Nevertheless, no general conclusions should be drawn in regard to the effectiveness of the treatment, since Hobby and her co-workers[18] and Fleming[4] have found strains of staphylococci with a very low sensitivity to penicillin. The frequency of the occurrence of insensitive strains in the eye cannot be judged in view of the small series examined.

The experimental results can be applied to human postoperative and posttraumatic purulent endophthalmitis only with great reservation. A few essential differences between the human infection and the experimental lesion must be emphasized. The size of the inoculum would be much smaller in the case of the human infection, but the interval between infection and treatment would probably be longer. In addition, there may exist primary involvement of deeper layers of the lens and of the posterior segment of the eyeball. The condition in infected human eyes is difficult to reproduce in animal eyes because of the higher incidence of spontaneous recovery in the latter. The results reported here are concerned with acute intraocular infections caused by a large inoculum. For this condition local application of penicillin is more effective than the combined sulfadiazine

17. Bellows, J. G.: Chemotherapy in Ophthalmology, Arch. Ophth. **29**:888 (June) 1943.

18. Hobby, G. L.; Meyer, K., and Chaffee, E.: Activity of Penicillin in Vitro, Proc. Soc. Exper. Biol. & Med. **50**:277, 1942.

therapy, although the latter may be of great practical value in treatment of milder staphylococcic infections of the human eye.

II. INFECTIONS WITH CL. WELCHII

The frequency of post-traumatic and postoperative intraocular infections with anaerobes is not known. Although only 27 cases have been reported in the literature, it is generally assumed that their occurrence is less rare than the number of published cases would indicate. Morax [19] saw 1 case of ocular infection with Cl. welchii following explosion of a grenade in World War I; he explained the scarcity of cases by the technical difficulties of the bacteriologic examination. A better judgment of the relative frequency of anaerobic infections of the human eye may be attained on the basis of their clinical diagnosis, as described by Ridley [20] and Hamilton [21] and especially stressed by Rieger.[22] It is believed that panophthalmitis generally follows an anaerobic infection of the eye.

Infections were produced in the eyes of rabbits by Chaillous [23] and Schumacher [24] and in extensive, systematic studies by Morax and Chiazzaro.[25] Schumacher produced suppuration of the anterior segment by the injection of an undiluted broth culture of Cl. welchii into the anterior chamber. The other authors did not produce any change or obtain more than transitory iritis with this technic. Morax and Chiazzaro, however, succeeded in producing almost regularly a severe endophthalmitis ending in panophthalmitis by injection of spores of various species of anaerobes into the lens. The observations reported in this paper confirm the results of Chaillous and of Morax and Chiazzaro.

PRELIMINARY EXPERIMENTS

The injection of Cl. welchii (0.05 cc. of a 10^{-1} dilution of an eighteen hour culture in thioglycollate broth) into the anterior chamber did not produce progressive endophthalmitis suitable as a test object. The technic applied successfully in experiments with pneumococci and staphylococci, that is, injury of the lens at the time of injection, also did not establish anything more than a self-limiting iritis of short duration. The intralenticular injection of Cl. welchii (0.05 cc of a 10^{-4} dilution in isotonic solution of sodium chloride) regularly produced purulent endophthalmitis of a subacute or chronic course, which was followed by complete destruction of the inner layers of the posterior segment of the eye. This method was a modification in minor points of that described by Morax and Chiazzaro.

The pupil was dilated with atropine and the eye anesthetized with a 0.1 per cent solution of nupercaine hydrochloride. A 27 gage needle was used to perforate the cornea at the limbus at 12 o'clock and was inserted obliquely in the

19. Morax, V.: Des infections du globe oculaire par microorganismes anaérobies, Bull. Acad. roy. de méd. de Belgique **7**:321, 1927.

20. Ridley, F.: Gas Gangrene Panophthalmitis, Tr. Ophth. Soc. U. Kingdom **49**:221, 1929.

21. Hamilton, J. B.: Notes on B. Welchii Infection of the Globe, Brit. J. Ophth. **14**:452, 1930.

22. Rieger, H.: Ueber Wundinfektion des Augapfels mit Erregern der Gasbrandgruppe, Arch. f. Ophth. **137**:61, 1937.

23. Chaillous, J.: Deux cas d'infection traumatique du globe oculaire par un microbe anaérobie (Bacillus perfringens), Ann. d'ocul. **134**:115, 1905.

24. Schumacher, G.: Anaërobe Bazillen bei Augenverletzungen, Klin. Monatsbl. f. Augenh. **46**:34, 1908.

25. Morax, V., and Chiazzaro: Sur l'infection du cristallin: Recherches cliniques et expérimentales, Ann. d'ocul. **164**:241, 1927.

anterior cortex of the lens in the pupillary area. The fluid was then injected into the region of the anterior pole.

The technic of treatment was the same as that in experiments with staphylococcic infections.

Preliminary experiments consisted of the in vitro determination of the sensitivity to penicillin of two strains of Cl. welchii and of the study of the course of the untreated infection after intralenticular injection of the dilution of the culture. Both strains were found to be relatively insensitive to penicillin, as 6.25 to 12.5 micrograms per cubic centimeter of a rather crude preparation of penicillin was necessary to inhibit the growth of a 10^{-1} dilution of an eighteen hour culture in thioglycollate broth with the serial dilution method of Fleming.[4]

The various stages of the infection were studied clinically and histologically in 20 control eyes, which were enucleated two to thirty-eight days after injection. The inflammatory signs attributable to the infection developed usually within forty-eight hours. At that time a moderate amount of purulent and fibrinous exudate was seen in the anterior chamber. Infiltrations of various extent were visible in the lens, and circumscribed patches of purulent exudate were noted on its posterior surface. During the first week the infection was generally confined to the cornea, lens, iris and ciliary body. After this the acute inflammation extended in most instances into the vitreous space, the optic nerve and the retina. As a rule the surface of the optic disk was the first area of the eyeground on which leukocytes accumulated. Detachment of vitreous was seen in the early and in the late stage of the infection. The signs of inflammation in the anterior segment often regressed after the third or fourth week. The injection of the eyeball disappeared; the anterior chamber became clear, and the contracted pupil was closed by an occlusion membrane. Dissection and histologic examination of the eye at this period disclosed an abscess of the vitreous, advanced disintegation of the lens and complete detachment of the retina. In a few instances the choroid was densely infiltrated before the retina was destroyed. The inflammation remained localized in the eye, and no signs of a systemic infection were noted during the period of observation.

Gram stains were made of all eyes. Verhoeff's method[5] gave better results than the Gram-Weigert technic and revealed the presence of a moderate or large number of morphologically characteristic gram-positive bacilli lying within the substance of the lens of all eyes. In many instances the capsule of the lens had been digested away, and infiltrated, necrotic lens material protruded into the anterior and posterior chambers or into the vitreous space. Apparently, the distribution of the bacilli depended in part on the pressure of injection and on the site of the needle tip during injection. In the early stage of the infection, however, foci of bacilli were seen in the anterior layers of the lens or in deeper parts of the anterior half. In later stages the foci were observed near the posterior surface or beneath the posterior capsule of the lens. The substance of the lens had lost its fibrillar structure in the areas of bacillary foci. Bacilli were frequently seen in great numbers at the border of the infiltration but rarely within the infiltrated area. They were not seen outside the lens or apart from the lens substance, and their number did not decrease noticeably in the later stages of the endophthalmitis.

RESULTS OF TREATMENT

Combined sulfadiazine therapy was used in 4 eyes and local penicillin therapy in 8 eyes. The second eye of each of the 12 rabbits was kept as a control. The clinical appearance of the eyes treated with the sulfonamide compound suggested a

beneficial effect in 1 eye and no effect in 3 eyes. The inflammatory process in 1 of the treated eyes advanced more rapidly than that in the control eye. No influence of the systemic treatment was evident on comparison of the control eyes of rabbits which received sulfadiazine orally with the control eyes of the animals not so treated. Three eyes of the penicillin series presented fewer signs of inflammation than their controls. The treated and untreated eyes of 3 other rabbits showed no differences, and in 2 rabbits the endophthalmitis appeared to have progressed further in the treated eyes than in the control eyes. The impression of a favorable effect of the treatment in 1 out of 4 rabbits in the sulfadiazine series and in 3 out of 8 rabbits in the penicillin series was not substantiated by the histologic examination of the posterior segments of the treated eyes. The infection had progressed behind the lens-iris diaphragm with the same intensity as in the control eyes despite the improvement of the endophthalmitis in the anterior segment.

At an early stage of the infection one eye of a rabbit in the penicillin series showed strikingly less infiltration and purulent exudate than the control eye after two days of treatment. On histologic examination the lens of this eye, as well as the lenses of all treated eyes, was found to have a large number of well stained, morphologically normal bacilli. It can be assumed, therefore, that the course of the infection was only delayed in this eye. No beneficial effect of the therapy was noticed in regard to the number or distribution of the bacilli and the extent of the infiltration in the lens.

COMMENT

The technic which was successful in establishment of a standard lesion with D. pneumoniae and Staph. aureus failed to produce a reliable test object of the anterior segment of the rabbit eye with Cl. welchii. Deleterious endophthalmitis was obtained only on injection of a dilution of the broth culture directly into the lens. The results of chemotherapy in experiments with Cl. welchii cannot be compared with those in the experiments with pneumococci and staphylococci because of the much more favorable experimental conditions in the latter.

Traces up to 1.3 mg. of the sulfadiazine drug per hundred grams of infiltrated lens were observed in 4 eyes after combined sulfadiazine therapy (one hour after iontophoresis and three hours after the oral administration of 0.25 Gm. per kilogram of body weight). Bellows and Chinn [26] reported 1.1 mg. of sulfapyridine per hundred grams of tissue and no sulfathiazole in the intact lens four hours after oral administration of the compounds. P'an [27] found 2.4 mg. of the sulfonamide drug per hundred grams of the lens after the local use of sulfapyridine but none after the application of sulfathiazole and sulfadiazine powder. It is reasonable to assume that penicillin enters the inflamed lens in the same moderate proportion as do the sulfonamide compounds. The experimental conditions for the effective treatment of infection with Cl. welchii were further impaired by the comparatively low sensitivity of the two strains to penicillin.

From the results of these experiments it appears unlikely that the treatment of anaerobic infections of the human eye involving deeper layers of the lens can overcome the twin disadvantages of the low susceptibility of the organisms to penicillin and the poor permeability of the lens.

26. Bellows, J. G., and Chinn, H.: Penetration of Sulfathiazole in the Eye, Arch. Ophth. **25**:294 (Feb.) 1941.

27. P'an, S. Y.: Ocular Absorption of Sulfonamide Derivatives After Local Application, Proc. Soc. Exper. Biol. & Med. **49**:384, 1942.

SUMMARY

1. Injections of various strains of Staph. aureus into the anterior chamber of the eyes of chinchilla rabbits with simultaneous injury of the lens produced a reliable standard lesion for chemotherapeutic experiments.

2. Combined oral and topical use of sulfadiazine was beneficial in 21.7 per cent of the eyes with purulent endophthalmitis produced by the aforementioned means when treatment was initiated six to seven hours after inoculation.

3. Penicillin, applied topically with the first treatment six to seven hours after inoculation, controlled the infection definitely in 62.5 per cent and possibly in 75 per cent of the eyes.

4. Intralenticular injections with Cl. welchii caused destructive endophthalmitis.

5. Neither sulfadiazine nor penicillin therapy begun six hours after the intralenticular injection of Cl. welchii had any effect on the resulting endophthalmitis.

Miss J. Di Grandi and Miss C. Zink assisted in this study.

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KERATITIS OCCURRING WITH MOLLUSCUM CONTAGIOSUM

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Molluscum contagiosum is an infectious disease of the skin characterized by the formation of multiple, small, discrete, umbilicated epithelial nodules. These nodules, appearing most commonly on the face and hands of young persons, are usually circular, average 2 mm. in diameter and are covered with normal epithelium. In the center of the characteristic umbilication is an orifice from which a cheesy mass consisting of ovoid cells, termed molluscum bodies, can be expressed. Microscopically these bodies are composed of swollen and vacuolated epithelial cells having an atrophic nucleus which has been pushed to one side by an acidophilic cytoplasmic inclusion body. These inclusions are composed of minute elementary bodies, first described by Lipschütz,[1] and are thought by some investigators to be the causative virus. The virus origin of molluscum contagiosum was established in 1905 by Juliusberg,[2] who demonstrated that the disease was transmissible from person to person by material which had passed through Chamberland filters.

Although molluscum contagiosum has been described as a relatively common cutaneous condition, it rarely appears on the eyelids; however, Elschnig [3] observed an incidence of 1 in 2,500 cases in the Eye Clinic at Prague, and Quill,[4] at the Mayo Clinic, reported that it affected the lids in 11 of 128 cases of the disease. In the clinic of this university only 3 cases have been encountered in the past fifteen years.

The appearance of molluscum contagiosum on the eyelids is similar to that elsewhere on the skin. Clinically, it must be distinguished from nevus, fibroma, verruca and epithelioma. The diagnosis is confirmed by microscopic examination of the excised lesions.

Molluscum contagiosum nodules along the margins of the lids may produce follicular conjunctivitis, an association first recognized by de Wecker [5] in 1896. Subsequent reports have shown that corneal complications, although rare, may also occur.[3] Elschnig,[6] in 1897, reported 7 cases of molluscum contagiosum of the eyelids, in 6 of which there was chronic conjunctivitis with multiple follicle formation closely resembling trachoma. The conjunctivitis disappeared after extirpation of the molluscum nodules. In a later report [3] Elschnig described a phlyctenular type of keratitis complicating the conjunctivitis. Gifford and Gifford,[7] in 1921, reported 6 cases of molluscum contagiosum of the eyelids in which there was secondary conjunctivitis. In 1 of these cases a corneal ulcer was present, which resisted ordinary treatment until the molluscum nodule

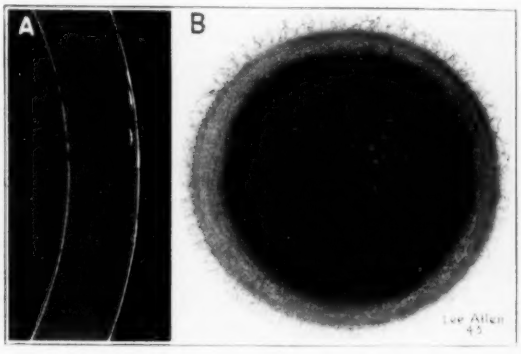

Fig. 1.—*A*, appearance of intraepithelial and subepithelial infiltrates with the narrow beam of the slit lamp; *B*, biomicroscopic appearance of corneal infiltrate.

was removed. Cavara [8] observed peripheral infiltration of the cornea, and a pannus-like lesion was described by Offret and Duperrat.[9] An unusual case was that reported by Quill,[4] in which a nodule of the lid was associated with a similar lesion of the cornea.

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1. Lipschütz, B.: Weitere Beiträge zur Kenntnis des Molluscum contagiosum, Arch. f. Dermat. u. Syph. **107**:387, 1911.

2. Juliusberg, M.: Zur Kenntnis des Virus des Molluscum contagiosum des Menschen, Deutsche med. Wchnschr. **31**:1598, 1905.

3. Elschnig, A.: The Significance of Molluscum Contagiosum as an Aetiological Factor of Conjunctival and Corneal Disease, Arch. Ophth. **51**:237, 1922.

4. Quill, T. H.: Molluscum Contagiosum of Eyelid and Cornea: Report of a Case, Proc. Staff Meet., Mayo Clin. **15**:139, 1940.

5. de Wecker: Klin Monatsbl. f. Augenh. **34**:64, 1896; cited by Gifford and Gifford.[7]

6. Elschnig, A.: Molluscum contagiosum und Conjunctivitis follicularis, Wien. klin. Wchnschr. **10**:943, 1897.

7. Gifford, H., and Gifford, S. R.: Molluscum Conjunctivitis, Arch. Ophth. **50**:227, 1921.

8. Cavara, V.: Le congiuntiviti da mollusco contagioso, Boll. d'ocul. **3**:1, 1924.

9. Offret, G., and Duperrat, R.: Les manifestations oculaires du molluscum contagiosum, Arch. d'opht. **2**: 993, 1938.

Thygeson,[10] in a recent paper on virus diseases of the eye, mentioned a case in which severe papillary conjunctivitis, superficial keratitis and pannus were associated with a molluscum nodule of the upper lid. The ophthalmia healed promptly after excision of the nodule.

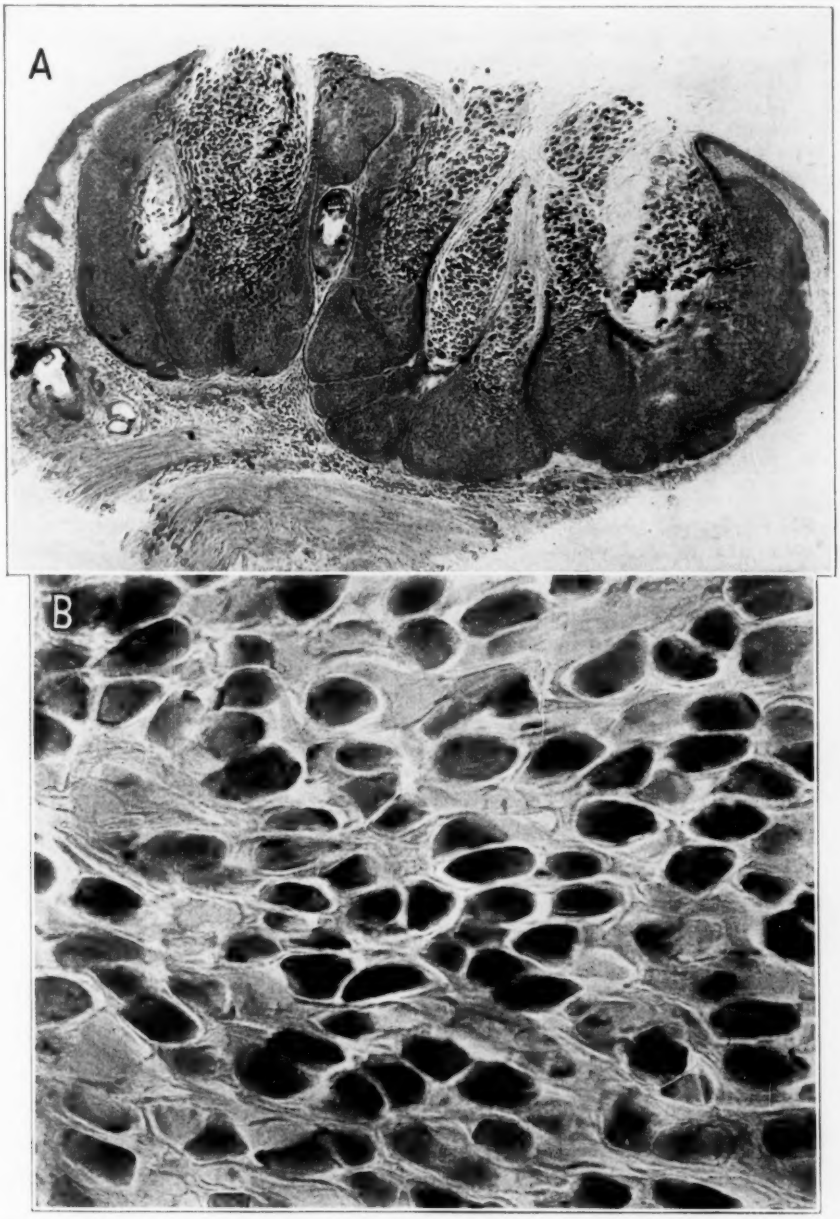

Fig. 2.—Photomicrographs of (*A*) a nodule of molluscum contagiosum (× 30) and (*B*) molluscum bodies (× 300).

REPORT OF A CASE

R. O., a man aged 24, was first seen in the ophthalmic clinic on Nov. 30, 1942, complaining of redness, slight itching, pain and crusting of the lid margins of the right eye during the past four days. The left eye was unaffected. Examination revealed the presence of diffuse hyperemia of the palpebral conjunctiva, which was more pronounced on the lower lid. There was a slight serous discharge. A tentative diagnosis of acute catarrhal conjunctivitis was made, and a collyrium composed of zinc sulfate, 0.25 per cent, in zephiran chloride (1:3,500) was prescribed. A forty-eight hour culture on blood agar of material from the conjunctival sac yielded no growth. The patient returned on December 5 with a number of flat conjunctival follicles in the lower cul-de-sac and a nontender, palpable preauricular gland. Because of the similarity of the condition to acute follicular conjunctivitis of the Béal type, the possibility of this disease was considered also. Culture of material on blood agar was repeated, but

10. Thygeson, P.: Viruses and Virus Diseases of Eye, Arch. Ophth. **29**:488 (March) 1943.

again no growth was obtained after forty-eight hours' incubation. Conjunctival scrapings stained with the Gram and the Giemsa technics revealed only a few epithelial cells with several monocytes and lymphocytes, but no organisms or inclusion bodies were seen. A collyrium containing isotonic solution of sodium chloride U. S. P. with epinephrine hydrochloride (1:1,000), 15 minims (0.93 cc.) to the fluid ounce (29.5 cc.), was prescribed, to be used three times a day. The patient returned, stating that he had improved under medication but that for the past three days there had been profuse lacrimation, severe photophobia, blepharospasm and the sensation of a foreign body in his eye. This was accompanied by slight pain and some blurring of vision.

Examination revealed the presence of edema and a large number of follicles in the conjunctiva of the lower eyelid and the inferior cul-de-sac. Also, a few follicles were seen in the conjunctiva of the upper eyelid in the canthal region. A faint circumcorneal flush was present. Examination with the biomicroscope showed the presence of a group of small subepithelial and intraepithelial corneal infiltrates, the latter staining faintly with fluorescein sodium (fig. 1). These infiltrates, eight to ten in number, were situated just nasal to the pupillary area of the cornea and had a diameter of about half that of a pinhead. Neither an aqueous flare nor floaters were observed in the anterior chamber. For the first time a small, round, yellow-tinged nodule, approximately 1.5 mm. in diameter, was seen on the margin of the lower lid. Umbilication could not be made out; yet the morphologic appearance of the lesion resembled that of a multilocular molluscum nodule. Nothing could be expressed from it by squeezing. It was thought to be either a nevus or a papilloma. Subsequent questioning of the patient revealed that the nodule had been noticed since the onset of conjunctivitis, five months previously, and that it had increased in size recently. Because of the absence of bacteria it was concluded that the condition was due to a virus infection. Its close similarity to epidemic keratonconjunctivitis in cases reported by Holmes,[11] Berliner [12] and others was noted. However, there was no edema of the lids or the bulbar conjunctiva, which is so characteristic of that condition. An attempt was made to culture the virus on the chorioallantois of the developing chick embryo, but without success. The results of culture and studies of smears were again negative. The patient was given phenocaine-epinephrine ointment and a pressure bandage to relieve ocular discomfort. Fifteen milligrams of riboflavin [13] was administered intramuscularly. This treatment was continued for five days, without any improvement in the patient's condition, and biomicroscopic examination revealed an increase in the number of subepithelial corneal infiltrates. The patient was referred to the department of dermatology, and a diagnosis of molluscum contagiosum was made. The nodule was then excised, and microscopic examination showed the typical histologic appearance of molluscum contagiosum (fig. 2). The patient's ocular complaints improved within twenty-four hours after removal of the nodule. In three days the subepithelial infiltrates could be distinguished only with difficulty, and when he was seen five days later, the patient was entirely free from ocular discomfort.

11. Holmes, W. J.: Epidemic Infectious Conjunctivitis, Hawaii M. J. **1**:11, 1941.

12. Berliner, M. L.: Epidemic Keratoconjunctivitis, Am. J. Ophth. **26**:50, 1943.

13. The riboflavin was given in the form of flavaxin niphanoid (Winthrop Chemical Company, Inc.).

COMMENT

Keratitis as a complication of molluscum contagiosum of the lid is rare, and the differential diagnosis may be difficult.

Although the occurrence of keratoconjunctivitis with molluscum contagiosum of the lid and its rapid cure following removal of the lesion may be known to many clinicians, it has received scant attention in the literature. The textbooks describe this disease as a disorder of the lid. No effect on the conjunctiva was mentioned by Norris and Oliver,[14] Ball,[15] Fuchs,[16] Atkinson,[17] Parsons [18] or Berens.[19] Conjunctivitis was noted by de Schweinitz,[20] Axenfeld [21] and Duke-Elder.[22] None of these authors described corneal involvement.

A review of the current literature showed that a conjunctivitis associated with molluscum contagiosum has been described by several authors. The condition is characterized by formation of follicles and sometimes papillary hypertrophy, at times so pronounced as to be confused with trachoma. In only 6 cases were corneal complications reported, and the lesions were all dissimilar.

The initial impression in the case reported was that of acute catarrhal conjunctivitis. Later, follicular conjunctivitis of Béal's type was considered since the early clinical characteristics of this condition were present—i. e., acute or subacute onset with much inflammation but little secretion; mild, nonpainful preauricular adenitis; absence of inclusion bodies or pathogenic bacteria, and presence of large mononuclear cells in conjunctival smears. The appearance later of corneal complications, however, made this diagnosis improbable. The resemblance of the subepithelial infiltrates to those appearing in cases of epidemic keratoconjunctivitis was noted, and for a time it was believed the condition

14. Norris, W. F., and Oliver, C. A.: A Text-Book of Ophthalmology, ed. 2, Philadelphia, Lea Bros. & Co., 1900.

15. Ball, J. M., Jr.: Modern Ophthalmology, Philadelphia, F. A. Davis Co., 1904.

16. Fuchs, E.: Text-Book of Ophthalmology, authorized translation from the twelfth, revised and greatly enlarged German edition by A. Duane, ed. 8, Philadelphia, J. B. Lippincott Company, 1924.

17. Atkinson, D. T.: External Diseases of the Eye, Philadelphia, Lea & Febiger, 1934.

18. Parsons, J. H.: Diseases of the Eye, ed. 2, New York, The Macmillan Company, 1936.

19. Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936.

20. de Schweinitz, G.: Diseases of the Eye, ed. 10, Philadelphia, W. B. Saunders Company, 1924.

21. Axenfeld, T.: Lehrbuch und Atlas der Augenheilkunde, ed. 8, Jena, Gustav Fischer, 1935.

22. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2.

might be of this type. However, with the diagnosis of a molluscum nodule on the lid and rapid resolution of the keratoconjunctivitis following extirpation of the lesion, the cause of the ocular condition became evident. In this case the molluscum nodule was missed during the earlier days of treatment. Later, even when it had been seen, absence of the characteristic umbilication and inability to obtain any cheesy material on expression gave the impression that the lesion might be either a nevus or a papilloma. The difficulty in differential diagnosis of these three conditions has been pointed out by other observers.[23] The nodule may be definitely identified as that of molluscum contagiosum only when the presence of molluscum bodies can be demonstrated microscopically.

The mechanism of production of conjunctivitis and keratitis in cases of molluscum contagiosum is not yet clearly understood. Thygeson [10] expressed the belief that the desquamating material from the molluscum nodule contains a toxic substance which produces the inflammation.

In order that the possibility that a molluscum nodule is the underlying cause of a recalcitrant conjunctivitis or keratoconjunctivitis may not be overlooked, all nodules on the margins of the lids should be viewed with suspicion when they are associated with inflammation of the conjunctiva and cornea. Excision of such nodules for microscopic study should be done whenever possible.

University Hospital.

23. O'Brien, C. S., and Braley, A. E.: Common Tumors of the Eyelids, J. A. M. A. **107**:933 (Sept. 19) 1936. Quill.[4]

TUBEROUS SCLEROSIS

REPORT OF A CASE

ERNEST F. KRUG, M.D.
WITH THE ASSISTANCE OF FRANCIS A. ECHLIN, M.D.
NEW YORK

REPORT OF CASE

History.—G. R. a boy then 6 years old, was first brought to me in 1929 for removal of a facial rash and correction of the right upper eyelid. I noted that he had an angioma of the right upper lid, measuring about 6 by 10 mm., and that his face—both cheeks and the nose—was covered with a reddish brownish rash. Each small nodule apparently had a fine vascular loop. Careful ophthalmic examination, with instillation of drops, revealed that he was slightly far sighted; otherwise, his eyes were normal. The fundi were normal, and vision was 20/20 with a + 0.75 D. sphere.

He was referred to a dermatologist, but the diagnosis of adenoma sebaceum was not made. The dermatologist suggested electrolysis for removal of what was apparently a congenital lesion, but permission for this was refused.

I saw the patient again in 1936, when an examination of the eyes showed less hyperopia, clear media and normal fundi. The next examination was in November 1940. He had had some attacks of vertigo. The outlines of the disks were slightly blurred, but vision was 20/20 in each eye. Inspection of the visual fields gave no information. The possibility of a lesion of the brain led me to ask for a general neurologic and a roentgenologic examination. Permission for both was refused.

In March 1941 he was brought to me with the history of progressively severe headaches following epileptiform attacks, which had come on with increasing frequency.

In the interim he had been under the treatment of a rhinologist for a condition diagnosed as chronic sinusitis. He had lost a great deal of weight and looked in poor condition. Vision was reduced to 20/200 in the right eye and to 20/100 in the left eye. Examination of the fundi showed papilledema (3 to 4 D.) in both eyes, greatly contracted visual fields and a central color scotoma in the right eye.

I insisted on a roentgenographic and a neurologic examination, and the patient was referred to Dr. Francis A. Echlin, at the Lenox Hill Hospital. The neurologic examination showed that the boy was alert, well oriented and cooperative but irritable and somewhat facetious. There was no definite impairment of memory and no signs of aphasia. The sense of smell was intact. He was admitted to the Lenox Hill Hospital on March 5, 1941.

It was apparent that something must be done for him, as his fainting spells and headaches were becoming very frequent, appearing without warning and characterized by weakness and loss of control of the limbs and mental confusion. There was not complete loss of consciousness, and he displayed definite convulsive movements. Since January 1941 he had had several attacks of forceful vomiting.

There was no evident impairment of intellectual ability, but his speech had become thick and stumbling. Prior to 1940 he had been well and had attended school, and his grades were good. He had lost 40 pounds (18.1 Kg.) in weight.

Since birth there had been some rash on the face; this had developed gradually into a lesion of adenoma sebaceum. At the age of about 2 years the lesion was of the characteristic butterfly type, involving the sides of the cheeks and the nose.

Physical Examination.—The patient, now aged 17, was well developed. General physical examination revealed an essentially normal status except for several cutaneous lesions, the most extensive of which was a butterfly-shaped area involving the cheeks and nose (fig. 1). This lesion was adenoma sebaceum, similar to ones associated with tuberous sclerosis. A few nodules were present on the forehead at the hair line, and the chin was also somewhat involved. Another lesion, resembling that of the face and measuring 6 or 7 cm., was present in the lumbar region. The patient was alert, well oriented and cooperative but irritable.

The fundi showed complete obliteration of the margins of the disks, with about 4 D. of papilledema and scattered hemorrhages. There was no hemianopsia, but the visual fields were constricted for both form and color. The pupils were large but equal and regular and reacted to light and in accommodation. There was no nystagmus, and extraocular movements were normal. Upward gaze was not limited.

Neurologic Examination (Dr. Francis Echlin).—There was no facial asymmetry, and hearing was normal. The remaining cranial nerves were intact. Motor power was everywhere normal, and there was no atrophy or fibrillation. Muscular tone appeared good. Coordination was not affected. Gait was normal, and the patient walked without swaying. The sensory system was intact. The impression was that of an expanding intracranial lesion.

Since the absence of cerebellar or lateralizing signs and the history of sudden episodes suggested intermittent obstruction of the foramens of Monro or the aqueduct of Sylvius, a tumor of the third ventricle was considered, and the cutaneous lesion on the face made the diagnosis of tuberous sclerosis a possibility.

Roentgenographic Studies (Dr. Frank Huber).—Roentgenograms of the skull, taken on March 5, were reported on as follows: Some increase in intracranial pressure was manifested by a slightly greater prominence of the convolutional markings and slight separation of the coronal suture. The sella turcica was deepened, and there were some decalcification and atrophy of both the anterior and the posterior clinoid processes. Midway between the foramen magnum and the vertex, apparently slightly to the right of the mid-

From the Surgical Service of Lenox Hill Hospital.

Read at the Seventy-Ninth Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 11, 1943.

line, were irregular, small areas of calcification within the structure of the brain. The pineal shadow was not definitely visualized. Small areas of increased density were scattered throughout the bones of the skull. The nasal accessory sinuses were rather extensively developed. There was no evidence of a pathologic condition. The right optic canal was slightly larger than the left.

Ventriculographic Examination.—In view of the severe papilledema and the roentgenographic evidence, a ventriculographic examination was carried out in the usual manner. When the ventricular needle was passed into the posterior horn of the right lateral ventricle, clear fluid escaped under pronounced pressure. Fifty cubic centimeters of fluid was removed and replaced with air. A needle was then passed into the brain on the left side in the direction of the posterior horn of the lateral ventricle. At a depth of 4 cm. it entered a cavity containing canary yellow fluid. Twenty-five cubic centimeters of this fluid was removed and was replaced with 10 cc. of air. No air escaped when the needle was first placed in this cavity.

Since the cavity which was tapped in the left cerebral hemisphere contained yellow fluid and no air, the lesion must either have been a cyst or an obstruction of the left lateral ventricle so that it was no longer in communication with the right ventricle.

Roentgenograms taken at this time showed a small amount of air in the left lateral ventricle, with notable dilatation of the right lateral ventricle and a filling defect in the medial aspect of the floor of the body of this ventricle.

While the patient was on the x-ray table the ventricular needle was again placed in the left lateral ventricle, and 70 cc. of yellow fluid was removed and replaced with a smaller quantity of air. Roentgenograms taken at this time showed rather pronounced and fairly symmetric dilatation of both lateral ventricles (fig. 2).

A rounded filling defect measuring slightly more than 2 inches (5 cm.) in its anteroposterior diameter, was seen in each lateral ventricle near the junction of the body and the anterior horn. The defect protruded into the ventricle from its inferior medial aspect. Small, irregular calcifications were seen in the defect on each side. There was no air in the third ventricle. The ventricular system did not show significant lateral displacement. The results of examination indicated that a mass blocked the foramens of Monro and probably obliterated the third ventricle. It also protruded into the anterior portions of the bodies of the lateral ventricles (fig. 2).

Fig. 1.—Patient with adenoma sebaceum associated with tuberous sclerosis.

Because of the location of the cerebral tumor and the probability that the condition was tuberous sclerosis, a difference of opinion arose as to the efficacy of surgical intervention, and operation was delayed forty-eight hours. Dr. Byron Stookey and Dr. Cornelius Dyke were called in consultation. They confirmed the location of the tumor and agreed that operation should be undertaken, especially since it was evident that the patient otherwise could not live more than a few weeks.

Operation (Dr. Francis A. Echlin).—On March 9 craniotomy and removal of the neoplasm were performed.

Before the dura was opened, it was noted that the brain was under considerable pressure. This was relieved by tapping the right lateral ventricle. When the dura was opened, numerous small, grayish plaques were visible in the cortex. These plaques did not deform the convolutions but appeared to be gliomatous.

On palpation, the cortex everywhere felt lumpy. There appeared to be normal areas of brain and many small, firm, whitish plaques, approximately 0.75 to 1.5 cm. in diameter. It was these plaques which gave the lumpiness to the cortex. Biopsy of this tissue was not made. A tumor was seen bulging from the region of the third ventricle into the medial wall of the right lateral ventricle, at the junction of the body and the anterior horn and in the region of the foramen of Monro. The medial wall of the neoplasm was bluish, and when the mass was opened, it was observed to contain soft tumorous tissue, resembling that seen in some medulloblastomas. This tumor was soft enough to be removed with ease by suction. After removal of the mass its medial, as well as its anterior, wall appeared to be surrounded by a capsule. When this capsule, which may have been the septum pellucidum, had been removed, one could see with ease into the left lateral ventricle and the anterior part of the third ventricle.

The choroid plexus appeared normal in both the right and the left lateral ventricle, and no other nodules on the walls of the ventricles were visible. The tumor

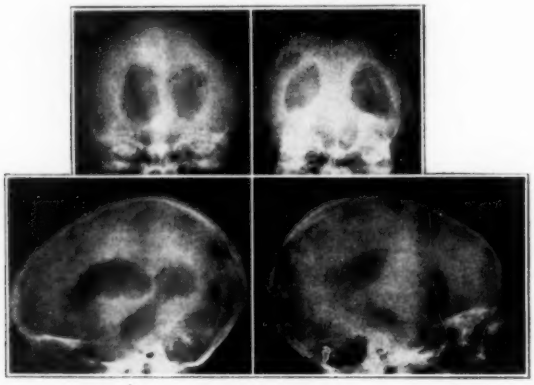

Fig. 2.—Roentgenograms of the skull in a case of tuberous sclerosis.

seemed to have been removed in its entirety. It apparently lay in the anterior part of the third ventricle and bulged upward and laterally into both lateral ventricles. It was approximately 2¼ inches (3 cm.) in diameter.

The patient left the table in fairly good condition. He was given a transfusion of 500 cc. of blood during the operation.

Microscopic Examination of Tumor (Dr. L. D. Stevenson).—Sections of the tumor were made at the department of pathology of Bellevue Hospital.

The material submitted contained a great deal of fibrous tissue (collagen) and in places groups of tumor cells, as illustrated in the sections. Nissl's method revealed that these cells often contained a nucleus and a well defined nucleolus. The cells were irregularly pear shaped—in many instances the cytoplasm trailed off into a process. Occasionally more than one process was visible. The cells resembled those seen in some of the nodular masses in the brain in cases of tuberous sclerosis (fig. 3).

Postoperative Course.—Convalescence was relatively smooth at first except for a rise of temperature to 105 F. on the day of operation. On the first postoperative day the temperature was 101.4 F.; the patient called me by name and moved the right arm and right leg freely on request. However, hemiplegia was present on the left side. On the third day after operation he was alert and rational; the decompression area was flat and pulsating, and the spinal fluid pressure on lumbar puncture had dropped to 140 mm. Left hemiplegia persisted, however. The course was one of slow improvement until March 22. There had been gradual return of motor power in the left arm and the left leg, and the patient was moving these extremities freely at this time. Power in the right arm and the right leg remained normal. There had, however, been fluctuations in the temperature to 103 F. during this period, but there was nothing to suggest infection of the wound, which had healed promptly, or of the spinal fluid.

On March 22 the patient became drowsy, and it was noted that he did not move any of his extremities. The temperature rose to 103 F. on March 24 and to 104 F. on March 25. For the next three weeks the course was stormy. It was believed that thrombosis of the longitudinal sinus had developed, perhaps at the time of operation as a result of traction of the brain on the sinus when the greatly distended ventricular system collapsed on the release of pressure. The patient became drowsy and almost completely out of contact with his surroundings. Generalized increase in tone developed in all the extremities, with loss of power, complete in the legs, bilateral grasp reflexes and a bilateral Babinski sign. During these three weeks there was irregular fever but no other sign of infection. He also began to have frequent attacks in which he showed the extensor rigidity of opisthotonos, with clenching of the fists (but not pronation of the wrists) and increase in the respiratory rate. These attacks occurred frequently when he was irritated and appeared more like a "sham rage" reaction than true decerebrate rigidity. In the intervals between attacks he was drowsy and irritable when questioned.

During his stay in the hospital he was given six roentgen treatments, with a total dose of 1,800 r, but the therapy was discontinued because of an unfavorable reaction.

Although the course of illness was still stormy, improvement began on April 3 and continued until his discharge from the hospital, on May 22. Power gradually returned to his arms. This improvement occurred first in the distal portion of the arms, and only later in the shoulder girdles. Power in the left leg also returned slowly, but there was little improvement in the function of the right leg. Visual acuity remained poor, and the disks showed pronounced secondary optic nerve atrophy. Mentally he became alert and well oriented. His conversation was intelligent, and he began to take a normal interest in his surroundings. Memory, however, remained imperfect.

It is now twenty-six months since operation. The patient is still confined to a wheel chair. His family believe that his mental state is about the same as before operation. He is alert, has a normal memory and takes a keen interest in his surroundings, in music and in world events. Judgment is perhaps impaired, and there is tendency to facetiousness. Motor power, as well as skilled movements, in the upper extremities is normal. There is moderate weakness of the left leg, but the right leg still shows considerable loss of power. He has had several minor attacks strongly suggestive of epileptic seizures, but none has occurred since he

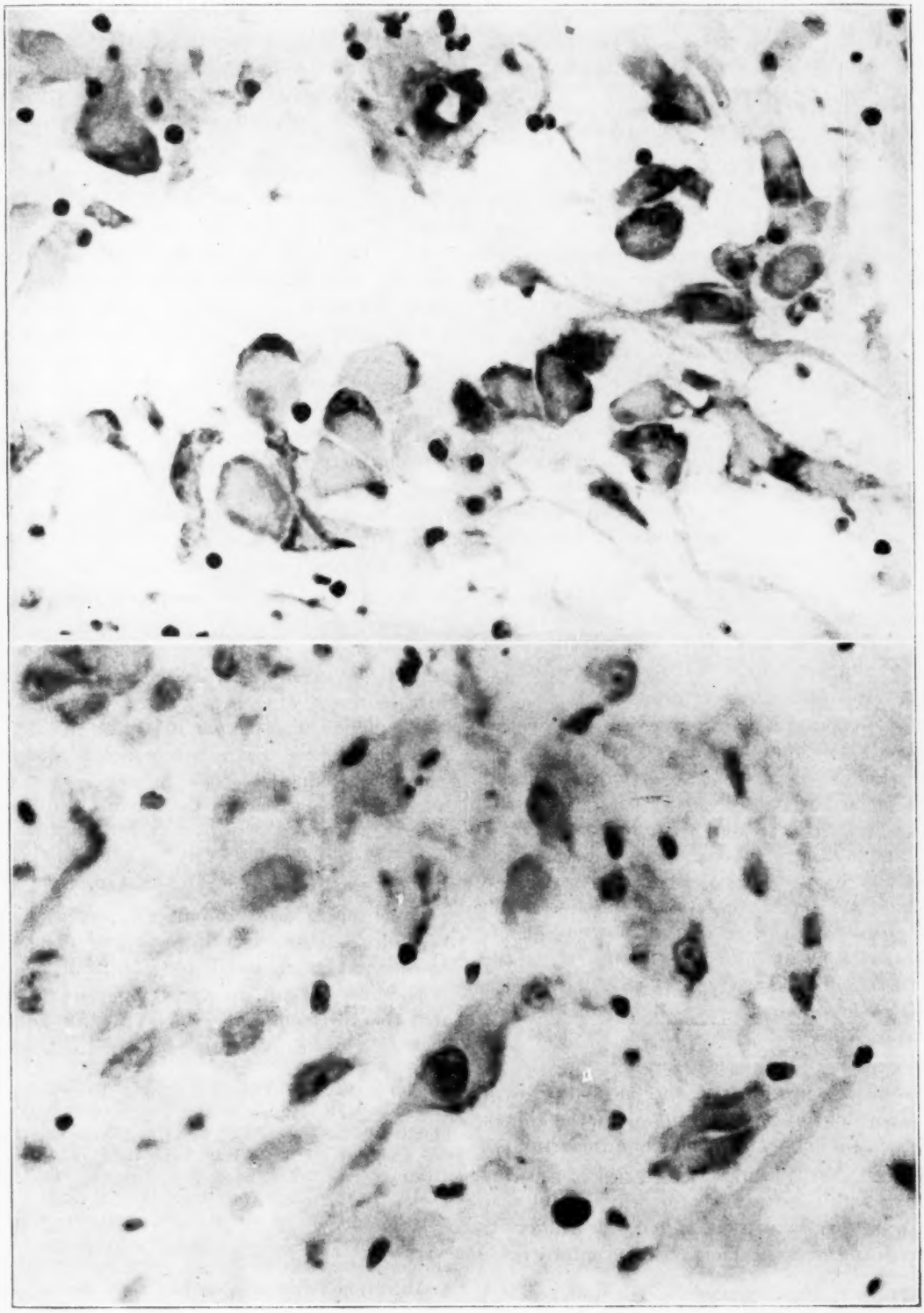

Fig. 3.—Microscopic sections of the tumor in a case of tuberous sclerosis.

was placed under sedation with phenobarbital, nine months ago.

Visual Acuity.—At the last examination both disks were dead white, with blurred edges. There was secondary nerve atrophy. The patient had light perception in the right eye, and vision was approximately 20/50 in the left eye, with ability to read Jaeger type 7. He read the headlines of the newspaper slowly. The left visual field showed concentric contraction to about 20 degrees.

COMMENT

Tuberous sclerosis is a disease entity. The term was first used by Bourneville to describe a rare form of cerebral sclerosis, which occurred chiefly in children and young persons. Neurath's oldest patient was 35 and Vogt's 37 years old, but a rare case of the disease occurring at the age of 75 was reported by Niewenhuijse.

Vogt,[1] in 1908, established the clinical syndrome of mental deficiency, epilepsy and adenoma sebaceum. After the work of Vogt, many other cases were reported, and it became evident that incomplete forms of the syndrome may occur. It was recognized that the cerebral condition might exist in the absence of one, or even all, of the other clinical signs.

Tuberous sclerosis appears to be more frequent in European countries; almost all subjects have been of the white race, Jews and Gentiles being affected alike.

Adenoma sebaceum, or nevus sebaceus, is a disease of congenital origin, which in our case appeared early, but it may not become evident until adolescence; it is characterized by pinhead-sized, yellow or reddish, waxy papules, situated on the flush areas of the face. The rash seen in the present case of tuberous sclerosis was of the Pringle type. In this type the blood vessels are especially affected, the lesion being essentially an increase in the size of the sebaceus glands, accompanied by proliferation of connective tissue and increased vascularity. As in our case, dermatologic lesions may appear on the trunk or the extremities.

Tuberous sclerosis is so named because of the potato-like appearance of the morbid growth. Neoplasms of this type may appear in the kidney, the heart, the lungs, the spleen and the retina.

Schuster,[2] in 1913, described a case of tuberous sclerosis with adenoma sebaceum in a young man who was of normal intellect but was subject to epileptiform attacks. He also reported a case in which a youth aged 16 manifested adenoma sebaceum, epilepsy and signs of intracranial tumor during life. Autopsy revealed tuberous sclerosis with multiple renal tumors.

The signs of intracranial tension are evident in early adult life. The epileptiform attacks, in the form of petit mal, may be present for many years without gross mental defect. Involvement of the third ventricle is reported in most of the cases of increased intracranial pressure. The epileptiform seizures are an important symptom, both in typical and in atypical cases. All types of attacks may be encountered—grand mal, petit mal, jacksonian convulsions, fainting spells without convulsions and paroxysmal outbursts—but in the absence of all these manifestations a facial eruption should arrest the attention and suggest the presence of tuberous sclerosis. Papilledema at once suggests intracranial neoplasm. Experience in the present case indicates that if a surgically accessible tumor is shown in the encephalogram, its successful removal should prolong the life of the patient and relieve him of his headaches and other unpleasant symptoms.

Associated retinal tumors are comparatively rare (van der Hoeve [3]). The pathology of tuberous sclerosis is not discussed in this preliminary report. With Dr. Echlin, I hope to submit a further report after a few years' observation of this patient. The patient is still an invalid, and the question arises how much usefulness he will recover eventually. The literature has many excellent reports on this subject. Messinger and Clarke,[4] Globus, Strauss and Selinsky [5] and van der Hoeve [3a] described the pathologic conditions in the eye.

Tuberous sclerosis is an endogenous, hereditary disease. Its relation to general neurofibromatosis is frequently pointed out, but Niewenhuijse opposed this concept, expressing the belief that the two conditions were different not only in their clinical manifestations but in their ana-

1. Vogt, H.: Zur Pathologie und pathologischen Anatomie der verschiedenen Idiotieformen: II. Tuberöse sklerose, Monatschr. f. Psychiat. u. Neurol. **24**:106-150, 1908.

2. Schuster, P.: Die Beziehungen der sogenannten tuberösen Sklerose des Gehirns zur Dermatologie, Dermat. Wchnschr. **57**:1475, 1913.

3. (*a*) van der Hoeve, J.: Augengeschwülste bei der tuberösen Hirnsklerose (Bourneville), Arch. f. Ophth. **105**:880-898, 1921; (*b*) Eye Diseases in Tuberous Sclerosis of the Brain and in Recklinghausen's Disease, Tr. Ophth. Soc. U. Kingdom **43**:534-541, 1923.

4. Messinger, H. C., and Clarke, B. E.: Retinal Tumors in Tuberous Sclerosis: Review of the Literature and Report of a Case, with Special Attention to Microscopic Structure, Arch. Ophth. **18**:1-11 (July) 1937.

5. Globus, J. H.; Strauss, I., and Selinsky, H.: Das Neurospongioblastom, eine primäre Gehirngeschwulst bei disseminierter Neurospongioblastose (tuberöse Sklerose), Ztschr. f. d. ges. Neurol. u. Psychiat. **140**: 1-29, 1932.

tomic changes. He stated that the tumors in the brain are small glial foci in the cortex, which have their counterpart in the occasional fibromas associated with tuberous sclerosis. Surely the picture is dependent on a congenital disturbance in the development of the undifferentiated neuroepithelial cells, which, according to the location in which they begin to grow—the central, the peripheral or the sympathetic nervous system—give rise to tuberous sclerosis or to neurofibromatosis or to a combination of the two conditions. Bielschowsky spoke of neurinomatosis centralis peripherica universalis. Reese [6] submitted an excellent article on the relation of tuberous sclerosis to drusen of the optic nerve, and Loewenstein and Steel [7] discussed the retinal lesions in this condition.

988 Fifth Avenue.

6. Reese, A. B.: Relation to Drusen of Optic Nerve to Tuberous Sclerosis, Arch. Ophth. **24**:187-205 (July) 1940.

7. Loewenstein, A., and Steel, J.: Retinal Tuberous Sclerosis (Bourneville's Disease), Am. J. Ophth. **24**: 731-741, 1941.

PUPILLOGRAPHIC STUDIES

V. PERIODIC SYMPATHETIC SPASM AND RELAXATION AND ROLE OF SYMPATHETIC NERVOUS SYSTEM IN PUPILLARY INNERVATION

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The syndrome of alternating spastic and paretic phases of a periodic (cyclic) nature in paralysis of the third cranial (oculomotor) nerve has frequently been observed since it was first described by Rampoldi, in 1884. In 1942 Lowenstein and Givner,[1] on the basis of pupillographic studies, showed that there is no real paralysis of the sphincter muscle and suggested therefore that the syndrome be spoken of no longer as a cyclic oculomotor paralysis but as an intermittent spasm of the third nerve with irregular periodicity (periodic spasmus mobilis oculomotorii). They showed that it is the result of partial destruction of the nucleus for the sphincter of the iris combined with supranuclear lesions, involving particularly the connections between the nucleus for the sphincter and the hypothalamus.

In contrast to this, periodic spasm of the sympathetic pupillary innervation has, to our knowledge, never been reported. In 1907 Westphal[2] described the phenomenon of transitory pupillary immobility to light and to near vision in cases of catatonia and hysteria and, later, in postencephalitic states. He observed that in a certain number of cases of catatonia this phenomenon was displayed: The pupil becomes dilated and no longer reacts either to light or in near vision. Such a phase of immobility may last for seconds, hours or even days. One of us (O. L.)[3] showed in 1920 that the phenomenon is of true sympathetic origin, since the spasms may be produced by such psychologic stimuli as pain and fear, which result in a long-lasting state of anxiety, common in catatonic and hysterical persons; it can, however, be observed in some normal persons of characteristic constitution (Bumke's anxiety pupils). Westphal later called this phenomenon spasmus mobilis pupillae. One of us (O. L.)[3] showed that it could regularly be abolished when the state of anxiety was allayed by suggestion of other emotions, such as joy. This spasmus mobilis of Westphal never showed a periodic nature.

The phenomenon we wish to describe is quite different from Westphal's spasmus mobilis. In particular, it is independent of psychologic conditions and is periodic.

REPORT OF A CASE

An unmarried girl aged 22 was first seen by one of us (A. L.) in the neurologic service of Dr. S. P. Goodhart at Montefiore Hospital. The family history, the history prior to onset of the present illness and the psychosocial history were noncontributory.

From the Department of Neurology, New York University College of Medicine.

This study was aided by grants from the Altman Foundation and the Oberländer Trust.

1. Lowenstein, O., and Givner, I.: Cyclic Oculomotor Paralysis (Spasmus Mobilis Oculomotorius), Arch. Ophth. **28**:821-833 (Nov.) 1942.

2. Westphal, A.: Ueber bisher nicht beschriebene Pupillenerscheinungen im katatonischen Stupor, Allg. Ztschr. f. Psychiat. **64**:694, 1907.

3. Lowenstein, O.: Experimentelle Beiträge zur Lehre von den katatonischen Pupillenveränderungen, Monatschr. f. Psychiat. u. Neurol. **47**:194, 1920.

Previous Course of Illness and Examinations.—On the patient's first admission to the hospital, on Sept. 16, 1936, at the Neurological Institute of New York, her complaints consisted of "progressive weakness of the muscles of the left arm and shoulder, occasional aching pain in the left shoulder and elbow joint, inability to straighten the left elbow joint completely and excessive sweating of the little finger of the left hand of two years' duration."

Physical examination at that time revealed well defined asymmetry of the two halves of the body, the left side being smaller than the right; a transient Horner syndrome on the left side; excessive sweating of the left side of the face with pilocarpine; almost constant excessive sweating over the distribution of the left ulnar nerve; a positive "manual Babinski" reflex [4] on the left; slight hypesthesia over the deltoid region of the left arm, and slight hyperreflexia of the left lower extremity.

The results of laboratory studies, including hematologic examination, urinalysis, examination of the spinal fluid, serologic tests and determination of the basal metabolic rate, were all within normal limits. Roentgenographic studies showed the presence of bilateral cervical ribs (larger on the right side than on the left) and a normal spine; an air encephalogram revealed nothing abnormal. Examination of the eyes on September 22, and again on October 9, disclosed a Horner syndrome on the left side. The patient was discharged for follow-up study after five weeks of hospitalization.

On second admission to the same hospital, on Dec. 8, 1936, the patient complained, in addition to the aforementioned disturbances, of a sensation of stiffness in the left arm and the left leg. She had been receiving roentgen therapy through the outpatient department. Examination now revealed excessive sweating over the left side of the face and in the palm of the left hand. The ophthalmologist reported that the "right pupil was still larger than the left." While the "reflexes in the left lower extremity were more active than those in the right," the reflexes in the right upper extremity "were a trifle more active than those in the left." There was an indefinite area of hypalgesia and hypesthesia over the left deltoid region. The other physical findings were the same as before.

The manometric reading of the spinal fluid now showed an initial pressure of 246 mm. (water manometer), with normal responses to jugular compression. After removal of 10 cc. of spinal fluid the pressure was 160 mm. She was again discharged.

The patient was again admitted to the Neurological Institute of New York on March 11, 1937, with the report of steady progression of symptoms. Now she definitely favored her right lower extremity when walking, and associated movements in the left upper extremity were diminished. There was decided weakness in extension and flexion of the left elbow and in abduction and adduction in the left shoulder. Babinski and Oppenheim signs were reported on the left side, with diminished abdominal reflexes on the same side. The other findings were the same as before, except that the sensory changes over the left deltoid region were no longer present. The results of laboratory studies were again within normal limits, with the protein content of the spinal fluid 23 mg. per hundred cubic centimeters.

On April 10 a cervical laminectomy (third to sixth cervical vertebra) was performed. The surgeon expressed the opinion that there was a "firm intramedullary tumor" at the level of the third to the sixth cervical neural segment. He was unable to rotate the cord and reported that on palpation "the entire cervical portion of the cord was extremely resistant." The cord was not split, and no material was taken for biopsy. The patient was discharged on May 7.

A fourth admission to the same hospital took place on June 1, 1937 because, toward the end of May, the patient began to walk "with shaking of the entire body" and numbness developed over the head and neck and between the shoulder blades. Physical examination now revealed a peculiar "undulating" gait, inability to perform equilibratory tests, dysmetria and asynergia in both heel to knee tests. In addition, there was adiadokokinesis on the left side. There was bilateral ankle clonus, with increased patellar and suprapatellar reflexes. Plantar responses were absent.

Her next admission was to the Brooklyn Jewish Hospital, on Feb. 8, 1938. Here the report indicated that "the left pupil was smaller than the right, the left palpebral fissure narrower than the right and the left eye slightly less prominent." Weakness was noted in both upper extremities (greater in the left than in the right), in the trunk muscles and in both lower limbs (greater in the left than in the right). There was a positive Romberg sign. The reflexes in the left lower limb were increased; the lower abdominal reflexes were absent, and an extensor response to plantar stimulation was noted on the left side. The patient was given another course of roentgen therapy. However, despite therapy, her condition became progressively worse.

4. Pool, J. L.: Manual Reflex: The Ulnar Adductor Reflex, Bull. Neurol. Inst. New York **6**:372-377, 1937.

Present Study.—She was admitted to the Montefiore Hospital on June 18, 1939. Examination at this time revealed a decided limp, with dragging of the left lower extremity. The left elbow was usually held in flexion, and there was a marked defect in the swing of the left arm. It was noted then that the fingers of the left hand were usually held in flexion but at times would straighten slowly and then flex again. A main en griffe was described. A Horner syndrome was present on the left. In addition, hyperalgesia was noted from the fourth lumbar to the second sacral dermatome on the left and, to a somewhat less marked degree, from the fifth lumbar to the second sacral dermatome on the right. The results of the rest of the examination were similar to those previously reported. Subsequent studies revealed that instillation of cocaine into the eyes caused dilation of both pupils, more on the left side than on the right. After a course of roentgen therapy, the patient appeared stronger; the few sensory changes disappeared, and she was discharged to the outpatient department. The results of laboratory studies were within normal limits. Definite improvement in gait was noted.

For one year her condition remained stationary, until about September 1941, when subjective weakness recurred in the left leg, as well as in the right arm. She was readmitted to Montefiore Hospital on Dec. 11, 1941. A peculiar gait was then described in which, with each step on the left side, the knee would buckle under and then would seem to catch itself and straighten out. The patient showed a tendency to walk mostly on the ball of the left foot. In addition, a "glove and stocking" type of sensory disturbance was noted on the left side, with hypesthesia, hyperalgesia and dysalgesia, dysthermesthesia and hypthermesthesia to both cold and to heat over the involved areas.

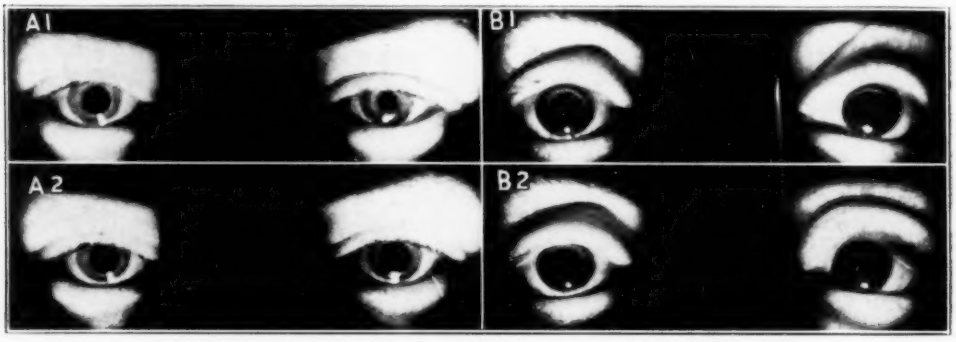

Fig. 1.—*A*, periodic sympathetic spasm and relaxation of the pupil. *1*, phase of sympathetic paresis when the left pupil is small. *2*, phase of sympathetic spasm when the left pupil is large. In *2* the palpebral fissure is widened as compared with that shown in *1*.

B, cyclic spasm and paralysis of the third nerve. *1*, phase of paralysis when the left pupil is large. The left upper eyelid is in ptosis and was held open by hand. *2*, phase of spasm when the pupil is small. The left eyelid opened spontaneously.

A tendency to flexor spasm of the ulnar three fingers on the left hand was noted. Other findings were hyperreflexia in the right upper and the left lower extremity and patellar and ankle clonus on the left side. Pathologic reflexes were definite on the left side and equivocal on the right side.

In January 1942 the ocular phenomenon to be described in detail later was first noted by one of us (A. L.) and has been studied exhaustively. The spasms of extension at the wrist and flexion of the ulnar three fingers occurring at irregular, but frequent, intervals were observed to become more intense and more frequent. These spasms were seen both in association with ocular changes (fig. 1 A_1 and A_2), preceding them by ten to twenty seconds, and independently. The reverse, i. e., ocular changes without the spastic contractions in the left hand, were never observed. Tests for sweating revealed no abnormalities, despite all previous subjective reports and objective observations. Studies of cutaneous temperature confirmed the gross observation that the left hand was warmer than the right and that the right foot was warmer than the left. Histamine tests (intradermal) revealed absence of the flare (loss of axon reflex) in the left foot and marked diminution of the flare in the left hand. The mecholyl chloride test (intradermal) revealed a much greater reaction in the right foot than in the left and a greater reaction in the left hand than in the right. Reflex changes in cutaneous temperature with the feet immersed either in hot or in cold water, under control, were normal on the left side and were greatly diminished on the right side.

The neurologic diagnosis was intramedullary disease of the cord, degenerative in character, most likely syringomyelia. The history, progress and present clinical picture spoke against the presence of neoplasm.

PUPILLOGRAPHIC STUDIES

1. PERIODIC DILATION OF THE LEFT PUPIL.

The left pupil underwent periodic dilation five to twenty seconds after the beginning of a spastic extension of the left wrist combined with flexion of the third, fourth and fifth fingers of the left hand. When the pupil began to dilate, the hand was already in a state of spasm. The pupillary spasm was never observed except when preceded by spasm of the hand and fingers. However, spasm of the hand developed without an ensuing pupillary spasm about once in twenty-five reactions.

A. Dilation Without Application of Drugs.—The periodic dilation occurred about once every five minutes; it consisted of the following phases:

1. A preliminary phase of very slow dilation, lasting about 1 to 1.5 seconds, with an extent of about 0.2 mm. and an average speed of 0.16 mm. per second.

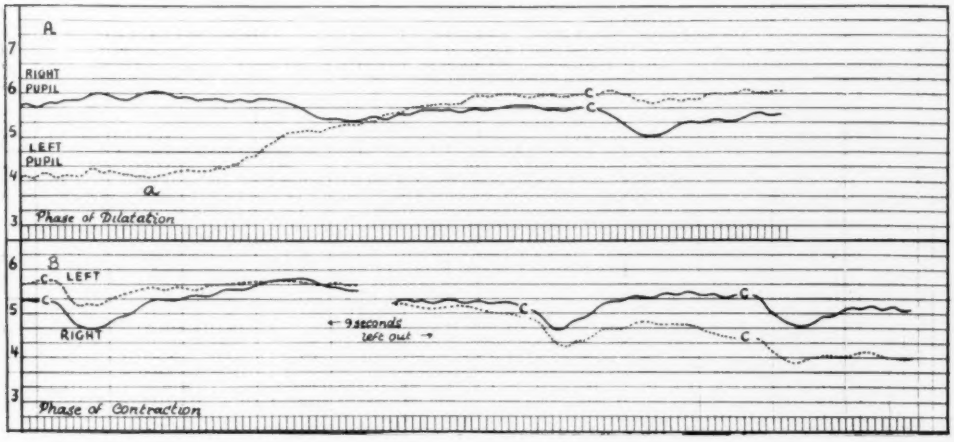

Fig. 2.—Spontaneous dilation and contraction of the left pupil.

A, phase of dilation beginning at *a*. *B*, phase of contraction. The continuous course of the curves is interrupted by several spontaneous lid closure reflexes (*c*, contraction and redilation). The lid closure reflex of the left pupil was diminished during the phase of dilation and increased as soon as active dilation was completed.

2. A primary stage of rapid dilation lasting about 1.4 to 1.6 seconds, with an extent of about 1.55 mm. and an average speed of 1 mm. per second.

3. A secondary phase of slow dilation, lasting about 2 to 3 seconds, with an extent of 0.2 to 0.3 mm. and an average speed of 0.1 mm. per second.

The maximal dilation was sustained about 5 seconds. Then a very slow contraction, lasting about 30 seconds, began. After approximately 15 seconds the left pupil was of about the same diameter as the right pupil, remaining at this level for about ten seconds. The left pupil then continued to contract beyond the extent of the right pupil for about 5 seconds longer, until it was about 1 mm. smaller. Closure of the lids during the primary phase called forth a normal reflex contraction of the right pupil; in the left pupil, however, it only retarded the pupillary dilation. A real closure reflex of the lid was not produced until the maximal pupillary dilation was reached, and was even then diminished.

When a light stimulus struck the eye during the period of active dilation, the light reflex elicited was less than during the phases in which the left pupil was either small or large. When, however, a light stimulus struck the eye during the period of active contraction, the light reflex elicited was greater than at any other time.

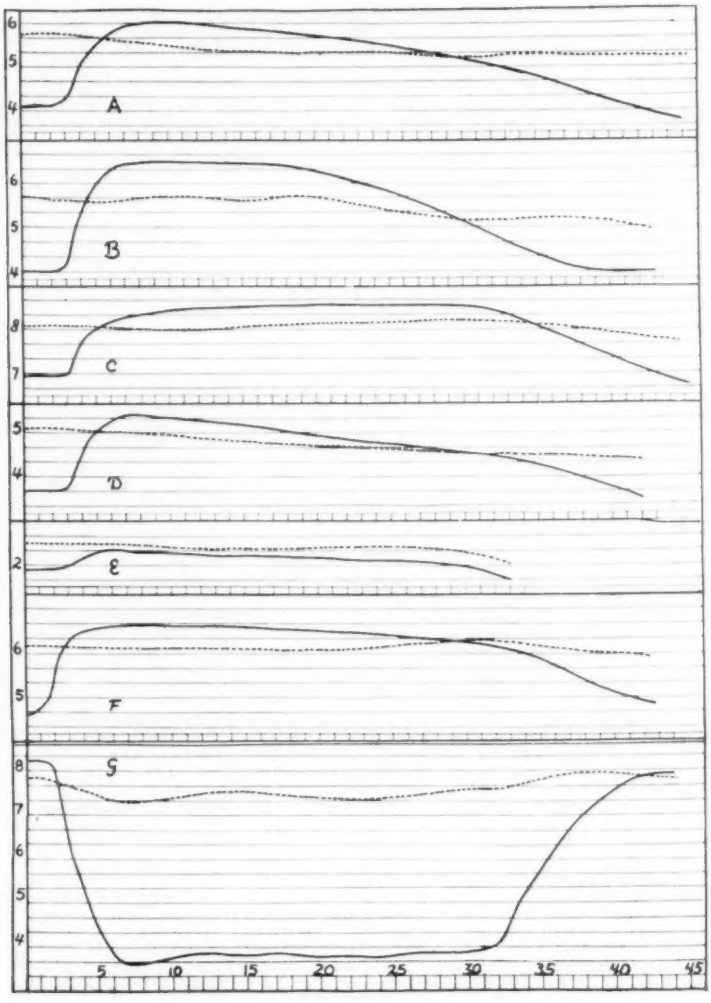

Fig. 3.—Spontaneous dilation and contraction of the left pupil without drugs and under the influence of drugs.

A, without drugs. *B*, fifteen minutes after the instillation of cocaine into the conjunctival sac. The speed and extent of dilation are slightly increased. The period of spastic dilation is prolonged. The rate of contraction is also increased. *C*, fifty-five minutes after the instillation of cocaine into the conjunctival sac. The pupillary diameter has increased to 6.8 mm. The period of spastic dilation is further prolonged. *D*, twenty-three minutes after the instillation of physostigmine into the conjunctival sac. The pupillary diameter has decreased to 3.7 mm. from its original 4.1 mm. The speed of dilation is not affected. The period of spastic dilation is slightly shortened. The preliminary phase of dilation, however, is absent. *E*, thirty-five minutes after the instillation of physostigmine into the conjunctival sac. The pupillary diameter has further decreased to 1.9 mm. The preliminary phase of dilation is absent. The average speed of dilation is decreased to 0.15 mm. per second. The period of spastic dilation is also decreased. *F*, effect of epinephrine. *G*, spontaneous contraction and dilation of the pupil in a case of periodic spasm of the third nerve (for comparison).

B. Dilation Under Influence of Drugs (fig. 3).—Cocaine Hydrochloride: Fifteen minutes after the instillation into the conjunctival sac of 3 drops of 1 per cent solution of cocaine hydrochloride the preliminary and primary phases were slightly accelerated but were not increased in extent. In the secondary phase, however, both the extent and the speed of dilation were increased to about twice their previous values (table). Forty minutes later, when the diameter of the pupil had increased from 4.2 to 6.8 mm., all stages of the periodic dilation were again decreased.

Dilation of the Left Pupil Without Drugs and After Application of Cocaine and Physostigmine

Condition	Pupillary Diameter, Mm.	Preliminary Phase of Dilation			Primary Phase of Dilation			Secondary Phase of Dilation			Total Dilation		
		Extent, Mm.	Duration, Sec.	Speed, Mm./Sec.	Extent, Mm.	Duration, Sec.	Speed, Mm./Sec.	Extent, Mm.	Duration, Sec.	Speed, Mm./Sec.	Extent, Mm.	Duration, Sec.	Speed, Mm./Sec.
Without drugs	4.1	0.2	1.0-1.5	0.16	1.55	1.4-1.6	1.0	0.3	2.0-3.0	0.1	2.05	5.25	0.4
Cocaine													
After 15 minutes	4.2	0.2	1.0	0.2	1.55	1.4	1.1	0.7	3.0	0.23	2.45	5.4	0.45
After 55 minutes	6.8	0.1-0.2	1.0	0.15	0.8	1.3	0.61	0.4	3.0	0.13	1.35	5.3	0.25
Physostigmine													
After 23 minutes	3.7		Absent		1.2	1.5	0.8	0.5	2.7	0.19	1.7	4.2	0.4
After 35 minutes	1.9		Absent		0.35	1.5	0.23	0.2	2.2	0.09	0.55	3.7	0.15

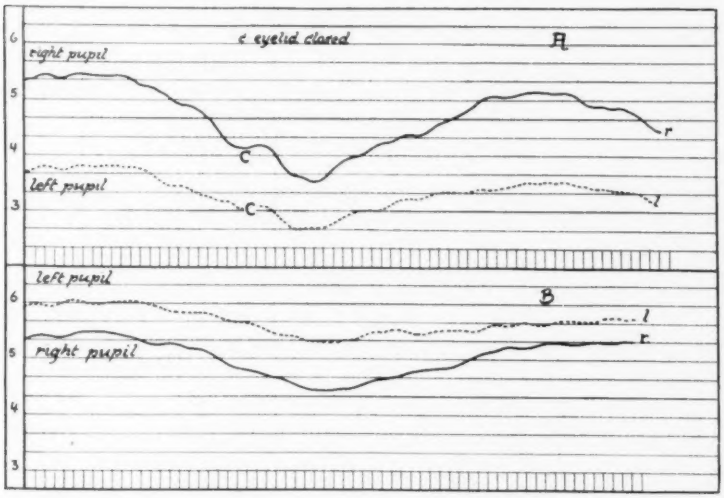

Fig. 4.—Nonperiodic spontaneous movements of both pupils.

A, when the left pupil is small; *B*, when the left pupil is large. Superimposed lid closure reflexes are represented by *c*. The spontaneous movements appear to be more extensive in *A* than in *B*.

2. Physostigmine Salicylate: Under the influence of physostigmine salicylate the preliminary phase disappeared entirely, and the primary and secondary phases decreased in speed, although not in duration.

Epinephrine Hydrochloride: The reaction was like that to cocaine, but to a lesser degree.

II. OTHER SPONTANEOUS PUPILLARY MOVEMENTS

Besides the so-called spastic periodic movements already described, both pupils performed other spontaneous movements. These were very slow vermiform contractions, occurring simultaneously in the left and in the right pupil.

In the right pupil they consisted of contractions about 1.5 mm. in extent at a speed of 1.3 mm. per second. When the left pupil was small, they consisted of contractions about 1 mm. in extent at a speed of 0.75 mm. per second. In the spastic phase of the left pupil, that is, when the pupil was large, they consisted of contractions of about 0.7 mm. in extent at a speed of 0.3 mm. per second. That is, these spontaneous movements were slower in the large than in the small phase of the left pupil (fig. 4). It appears, furthermore, that these spontaneous movements were less sluggish (0.49 mm. per second) when both pupils were under constant illumination than when they were in complete darkness. These movements involved both pupils and may be considered hippus.

Under the influence of cocaine, these spontaneous movements diminished both in frequency and in extent and finally disappeared after the pupillary diameter had reached more than 7 mm. Under the influence of physostigmine, however, they persisted, even tending to become less sluggish when the drug was beginning to take effect (after twenty-five minutes). They also persisted under the influence of epinephrine.

After the pupil had contracted to a diameter of 2.5 mm., the hippus became very sluggish in the left pupil and somewhat sluggish in the right pupil; it amounted in the left pupil to only 0.3 mm. at a speed of about 0.3 mm. per second and in the right pupil to 0.5 mm. at a speed of 0.5 mm. per second.

III. REACTION TO LIGHT

A. Without the Use of Drugs.—Both pupils reacted to light both directly and consensually. There were, however, characteristic differences between the two pupils, both when the left pupil was large and when it was small.

In analyzing the reflexes to light, one must bear in mind the fact that in normal reflexes to light the contraction follows a latent period of about two-tenths to three-tenths second. The contraction period consists of three phases: a primary phase of about 0.3 to 0.4 second and an average speed of about 5.5 mm. per second; a secondary phase of about 0.3 to 0.4 second and an average speed of about 2 mm. per second, and a tertiary phase (which is variable) of about 0.3 to 0.5 second and an average speed of 0.8 to 1.9 mm. per second. The whole contraction is carried on with an average over-all speed of 2.5 mm. per second (fig. 5).[4a]

We first state that in the case in question all speeds were far below these values both as to the primary and as to the secondary and tertiary phases of contraction.

4a. Gradle and Eisendrath (Klin. Monatsbl. f. Augenh. **71**:311-313, 1923) and Gradle and Ackerman (Reaction Time of the Normal Pupil, J. A. M. A. **99**:1334-1336 [Oct. 15] 1932) distinguish a primary and a secondary phase of contraction, the former appearing identical with our primary contraction phase, while the latter seems to include our secondary and tertiary contraction phases. They found a latency of 0.1875 second, a primary contraction phase of 0.4365 second at an average speed of 5.48 mm. per second and a secondary contraction phase of 0.3125 second at an average speed of 1.34 mm. per second. The whole contraction amounted to 2.82 mm.

with only one exception, the direct reaction of the right pupil, the primary contraction phase of which showed an average speed of 5.3 mm. per second. This is within the limits of normal. Secondary and tertiary phases of contraction in this case were below the normal values, although the speed of the whole contraction was still within the limits of normal.

The consensual reaction of the right pupil was approximately the same whether the directly stimulated left pupil was small or large. The time of contraction as

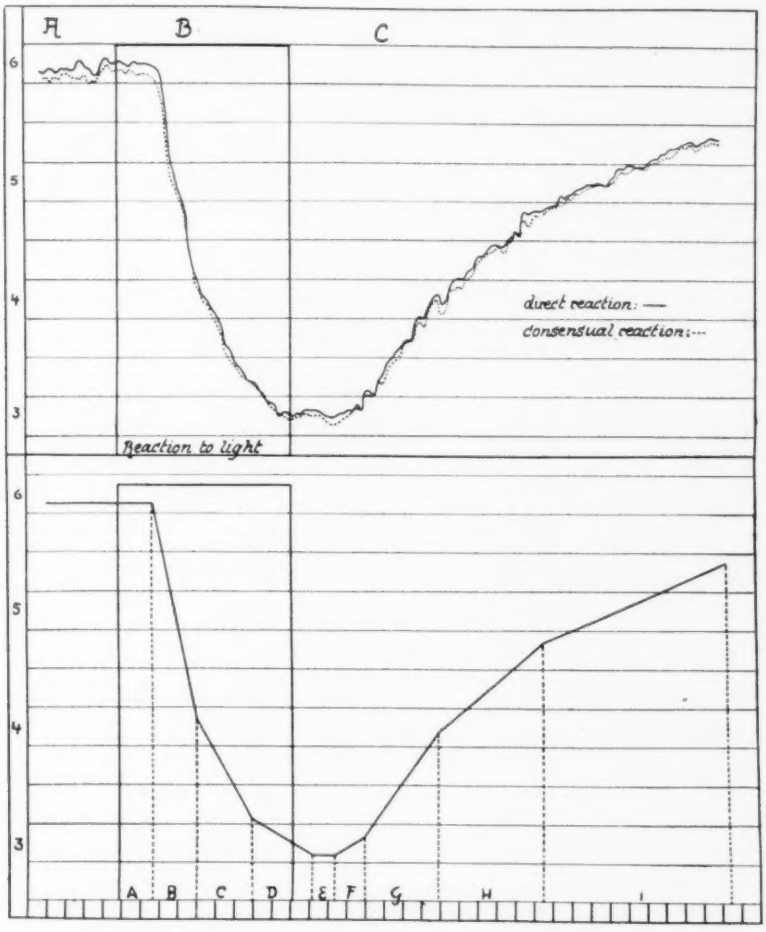

Fig. 5.—The normal reflex to light; method of interpretation.

First graph: *A*, pupils adapted to darkness, before stimulation with light. Note pupillary unrest. *B*, application of light stimulus (nine-tenths second) to one eye. Both pupils contract after a latent period. *C*, termination of light stimulus. Both pupils redilate after a second latent period.

Second graph (method of interpretation): *A*, latent period of contraction; *B*, primary phase of contraction; *C*, secondary phase of contraction; *D*, tertiary phase of contraction; *E*, latent period for redilation; *F*, preliminary phase of redilation; *G*, primary phase of redilation; *H*, secondary phase of redilation, and *I*, tertiary phase of redilation.

compared with that of the normal pupil was high, and the speed of the contraction was low; both values, however, were still within the limits of normal.

When the left pupil was small, its primary phase of contraction was normal; the secondary phase was decreased in extent, but not in duration, and the tertiary phase was absent.

When the left pupil was large, its primary phase of contraction was about equal to that of the same pupil when small, while the secondary phase was more extensive and the tertiary phase even longer and more extensive than the normal (fig. 6).

The consensual light reactions of the left pupil in all phases of contraction were equal to the direct reactions, both in the large and in the small phase.

The total contraction time was prolonged in both pupils.

B. With Cocaine (fig. 7).—1. Small Phase of Left Pupil: The direct reaction of the left pupil was not altered in its primary phase, but went on at a much higher speed and to a greater extent in its secondary and tertiary phases.

2. Large Phase of Left Pupil: The reactions of the left pupil slowed down and became less extensive in all phases (about one-half the extent of those in the small pupil).

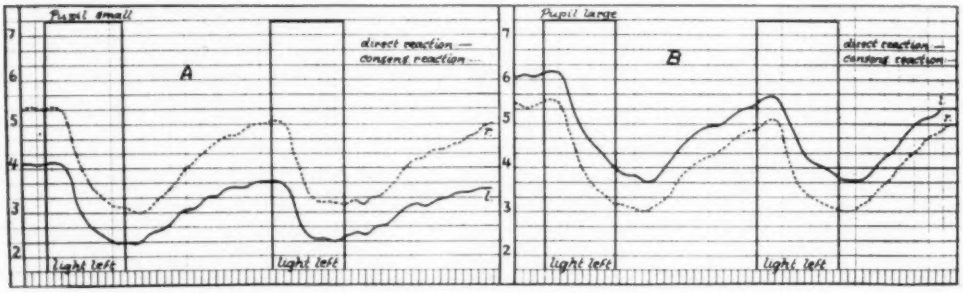

Fig. 6.—Reaction to light of the left pupil in large and small phases.

The solid line represents the directly reacting pupil; the dotted line, the consensually reacting one. *A*, small phase. The primary phase of contraction is normal; the secondary phase is decreased in extent but not in duration, and the tertiary phase is absent. These features are most pronounced in the second light reaction. *B*, large phase. The primary phase of contraction is normal; the secondary phase is more extensive and the tertiary phase is more extensive and longer lasting than in the corresponding phases shown in *A*.

The light reactions of the right pupil (both direct and consensual) were almost the same whether the left pupil was small or large. They were diminished in all phases by cocaine.

C. With Physostigmine.—Physostigmine diminished all light reactions of the left pupil.

1. Small Phase of Left Pupil: The primary phase of contraction was particularly diminished, the reaction becoming very slight and rather sluggish.

2. Large Phase of Left Pupil: Only the primary phase persisted; the secondary and tertiary phases were almost completely abolished.

IV. FATIGUE PHENOMENA

We have already emphasized that all the reactions in this case showed the features of fatigue from the beginning. They further showed increased fatigability to a series of light stimuli.

Reaction to Light of Left Pupil	Extent of Reaction of Left Pupil When Large, Mm.	Extent of Reaction of Left Pupil When Small, Mm.
First	2.47	1.5
Second	1.6	1.37
Third	1.47	1.23
Fourth	1.37	0.97
After psychosensory restitution		
Fifth	2.27	1.33

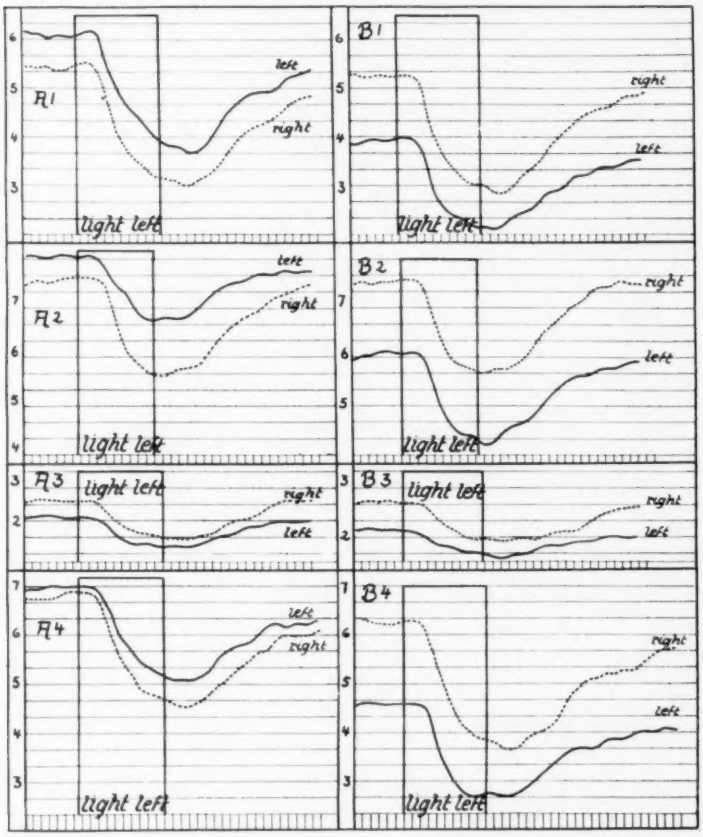

Fig. 7.—First line graphs: Without drugs. *A1*, when the left pupil is large. *B1*, when the left pupil is small.

Second line graphs: After instillation of cocaine. *A2*, when the left pupil is large. The reaction of the left pupil becomes slower and less extensive in all its phases. The static anisocoria increases during contraction (pseudo-oculomotor phenomenon). *B2*, when the left pupil is small. The primary reaction phase is not altered. The secondary and tertiary phases are more rapid and more extensive.

Third line graphs: After instillation of physostigmine. All reactions are diminished. *A3*, when the left pupil is large. The primary phase of contraction persists. The secondary and tertiary phases are almost completely abolished. *B3*, when the left pupil is small. The primary phase of contraction is diminished.

Fourth line graphs: After instillation of epinephrine. The slight change in pupillary reactions is more apparent in the large phase. It somewhat resembles the effect of cocaine.

As shown in this tabulation, the fatigue phenomena occurred much more readily when the left pupil was large than when it was small. The psychosensory

restitution phenomenon, however, was much more effective when the left pupil was large.

It is noteworthy that, in the course of the development of fatigue, tonohaptic reactions [5] sometimes appeared in the left pupil when it was small. The fatigue phenomena affected particularly the secondary and tertiary phases, both of them disappearing almost completely; this greatly diminished the time of contraction, which appeared limited to the primary phase of contraction. This phenomenon affected the left pupil when it was large to a lesser degree, although actually in the same manner. The left pupil showed the same kind of response in both the large and the small stage whether it reacted directly or consensually.

The directly reacting right pupil showed an equally increased fatigability.

V. REACTION TO PSYCHOSENSORY STIMULI

The right pupil reacted to sound to approximately the normal extent. After a latent period, a slow primary phase of dilation set in and was followed by a secondary rapid phase of dilation and a slow phase of recontraction (fig. 8).

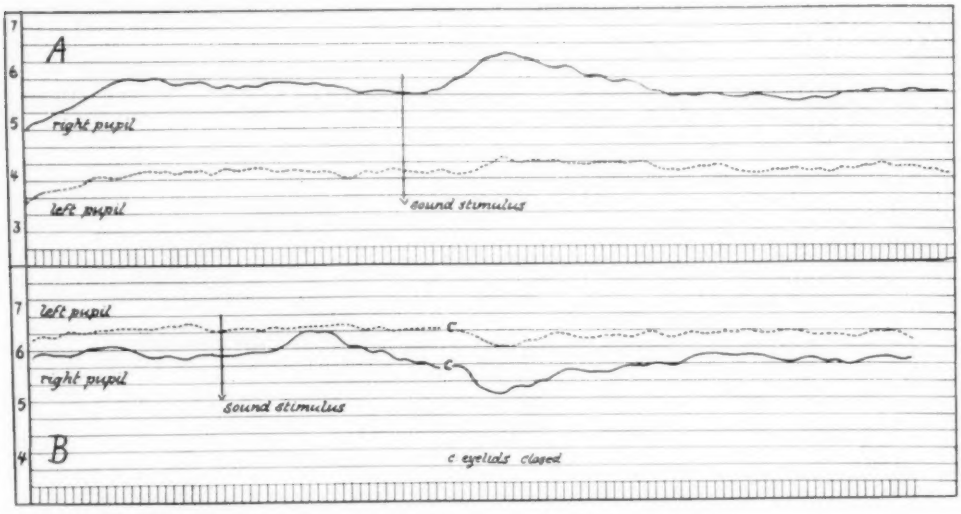

Fig. 8.—Influence of auditory stimulation.

A, small phase of left pupil. The reaction to auditory stimulation is present, but is diminished as compared with that of the right pupil. *B*, large phase of left pupil. There is no reaction on auditory stimulation. At *c* the course of the pupillary curve is interrupted by a lid closure reflex, more extensive on the right side than on the left.

1. The left pupil when small showed a pathologic reaction to sound stimuli; i. e., after an abnormally long latent period, decreased dilation appeared.

2. The left pupil when large was not observed to react to sound stimuli at all.

It is worth noting that in a case of cyclic oculomotor phenomenon,[1] psychosensory dilation was present but was diminished in both the spastic and the paralytic pupillary phase.

VI. PSYCHOSENSORY RESTITUTION PHENOMENON

As previously mentioned, a psychosensory restitution phenomenon existed both when the left pupil was large and when it was small. It was present to a greater degree in the large phase.

5. Lowenstein, O., and Friedman, E. D.: Present State of Pupillography: Its Method and Diagnostic Significance, Arch. Ophth. **27**:969-993 (May) 1942.

When the psychodilation and the spontaneous dilation phase of the left pupil coincided, the light reaction of the left pupil seemed diminished, so that the restitution phenomenon was apparently suppressed. On the other hand, when restitution was attempted during the contraction phase of the left pupil, the effect of the restitution phenomenon seemed to be increased (fig. 9).

VII. INFLUENCE OF DRUGS ON THE PUPILLARY DIAMETER

A. Cocaine.—Under the influence of cocaine, the normal pupil first contracted for a period of 5 to 7 minutes, or even more. This initial contraction was followed by the dilation proper.

The pupillary movements were measured after the instillation of 3 drops of 1 per cent cocaine hydrochloride (second drop three minutes after the first one, and the third drop seven minutes after the first one) both while the left pupil

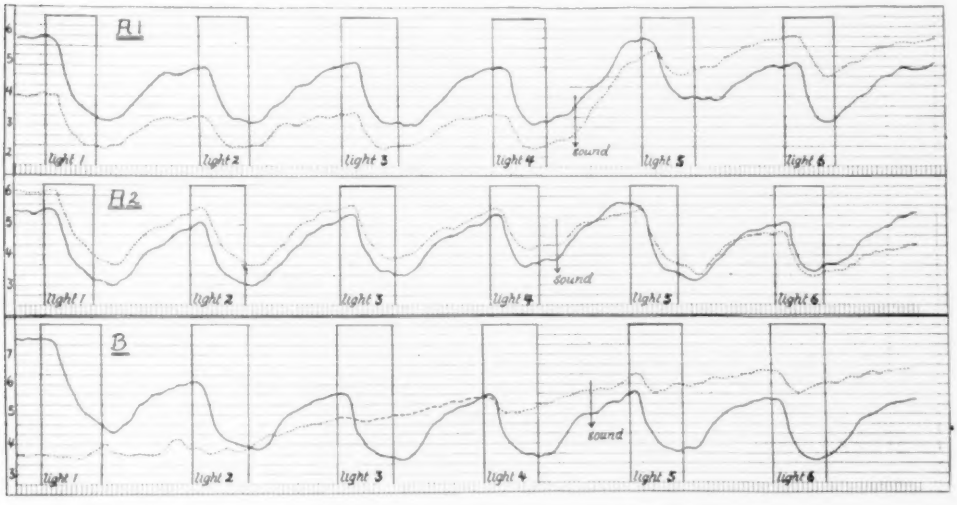

Fig. 9.—Comparison of reactions to light in the case of periodic sympathetic spasm and in a previously reported case of periodic parasympathetic spasm.

A, from the case of sympathetic spasm. *1*, small phase of left pupil. Four reactions to light, showing tendency to tonohaptic responses. A sound produced before the fifth light stimulus coincided with the spontaneous dilation of the left pupil, with production of a dilation of much greater speed than when the sound stimulus was not present. The psychosensory restitution phenomenon was absent as long as active dilation was going on (fifth reaction) but appeared as soon as the active dilation was completed (sixth reaction). *2*, large phase of left pupil. Four reactions to light, showing increased fatigability. Although the pupil was of about the same diameter at the beginning of the fourth reaction as at the beginning of the second, the contraction had been decreased to about two thirds of its earlier value. The auditory stimulus after the fourth reaction to light coincides with the contraction period of the left pupil. The fifth reaction to light is much more extensive than the fourth (about twice). *B*, from the case of cyclic spasm of the third cranial nerve. Contrary to what was found to be the case represented in *A1*, the case of cyclic sympathetic spasm, the sound stimulus did not cause an increase in the speed of the spontaneous pupillary dilation. In this case the psychosensory restitution phenomenon was practically absent in both the small and the large phase of the pupil.

was small and while it was large (fig. 10 *A1* and *B1*). In both stages the pupils showed reactions.

Phase of Left Pupil	Instillation of Cocaine in Both Conjunctival Sacs	Preliminary Contraction, Mm.	Dilation, Mm.
Small	Left pupil	1.0	2.1
	Right pupil	0.9	1.7
Large	Left pupil	0.35	1.45
	Right pupil	0.6	1.5

The significance of the results is as follows: The left pupil reacted to cocaine better in the preliminary and in the dilation phase when the pupil was small than when it was large. The right pupil showed the same feature to a lesser degree.

B. Physostigmine.—As in the normal pupil, the contraction of the pupil was preceded by a slight dilation. Both pupils reacted to physostigmine.

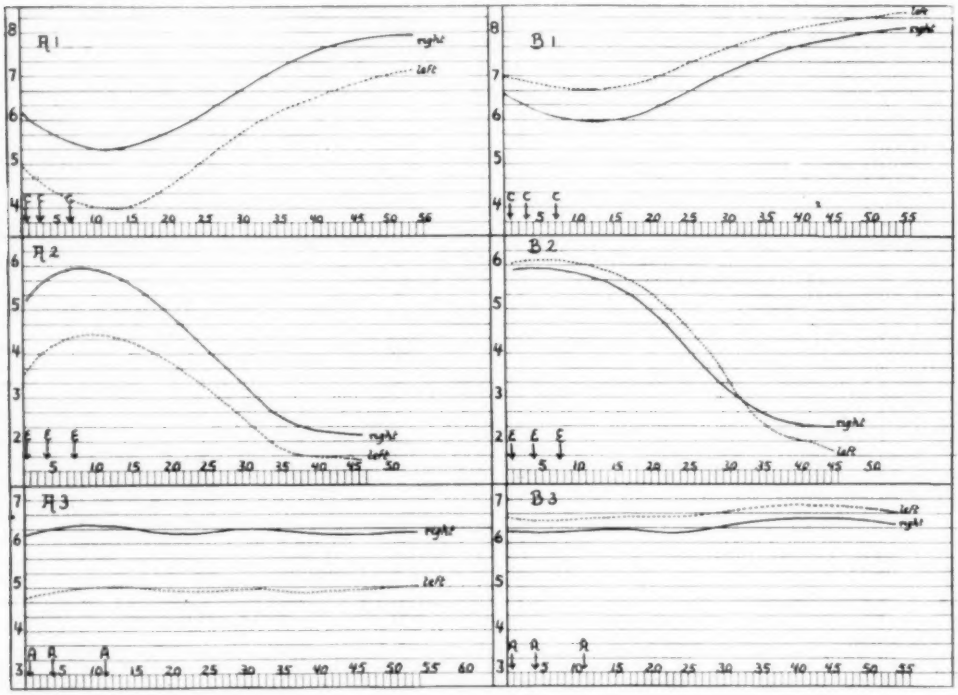

Fig. 10.—Influence of drugs on the size of both pupils during (*A*) the phase of dilation and (*B*) the phase of contraction of the left pupil. Arrows mark the time of instillation of the drug into the conjunctival sac.

First line graphs: Influence of cocaine, when the left pupil is small (*A1*) and when the left pupil is large (*B1*). In both cases, both the right and the left pupil dilate after an initial phase of contraction.

Second line graphs: Influence of physostigmine, when the left pupil is small (*A2*) and when the left pupil is large (*B2*). In both cases both the right and the left pupil contract after an initial phase of dilation.

Third line graphs: Influence of epinephrine, when the left pupil is small (*A3*) and when the left pupil is large (*B3*). There is no noticeable effect on the pupillary diameter.

Phase of Left Pupil	Instillation of Physostigmine in Both Conjunctival Sacs	Preliminary Dilatation. Mm.	Contraction, Mm.
Small	Left pupil	0.9	1.9
	Right pupil	0.8	3.0
Large	Left pupil	0.0-0.1	4.2
	Right pupil	0.0-0.1	3.6

The significance of these results is as follows: The left pupil reacted less to physostigmine in the contraction phase when the pupil was small than when it was large. The reverse was true for the phase of preliminary dilation to physostigmine.

The right pupil behaved similarly both to physostigmine and to cocaine, but to a lesser degree. This indicates that the right pupil was hypersensitive to cocaine and less sensitive to physostigmine when the left pupil was small. It was less sensitive to cocaine and more sensitive to physostigmine when the left pupil was large.

C. Epinephrine.—This drug had no influence at all on the pupils when the left pupil was in its small phase and no clearcut influence when the pupil was in its large phase. (Perhaps it caused a transitory dilatation of 0.33 mm. on the right side and of 0.2 mm. on the left side.)

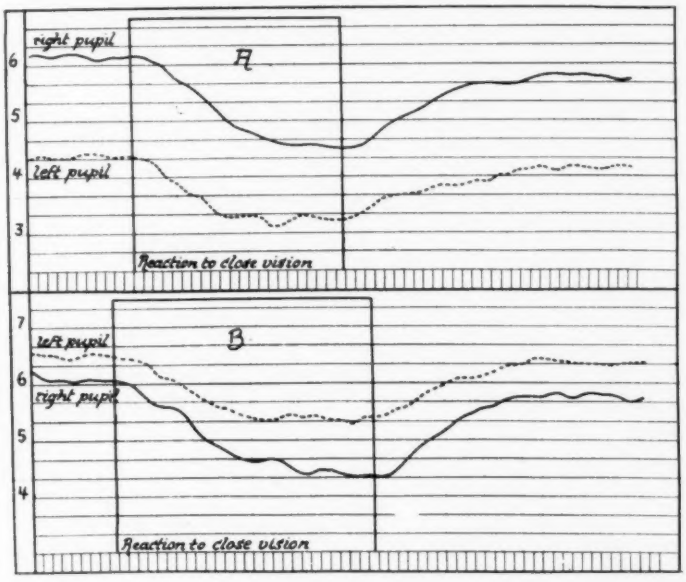

Fig. 11.—Reactions to near and far vision.

A, small phase, and, *B*, large phase, of left pupil. Note that the reactions to near vision are about equal in extent whether the left pupil is small or large. However, when the left pupil is large, contraction seems more sluggish and redilation is more prompt when the pupil is large than when it is small. Anisocoria decreases during redilation when the left pupil is large and increases when it is small. Anisocoria increases during contraction, however, when the left pupil is large and decreases when it is small.

VIII. REFLEXES TO CLOSURE OF LIDS (FIG. 2)

The reaction to closure of the lids, i. e., the contraction and redilation of the pupil following each full or partial closure of the lids, was well developed when the left pupil was in its small phase. In this phase it amounted to approximately 0.8 mm.

When the pupil was large, it was reduced to about one third of its former extent.

IX. REACTION TO NEAR AND FAR VISION (FIG. 11)

A. Large Phase of Left Pupil.—The contraction to near vision amounted to approximately 2 mm. in the left pupil and approximately 2.3 mm. in the right

pupil. The reaction to near vision in the left pupil increased when the convergence movement coincided with the phase of contraction of the left pupil. In that case, the relation of the contraction of the left pupil to that of the right pupil may be 2.16 : 2.5.

B. Small Phase of Left Pupil.—The contraction of the left pupil amounted to 1.1 mm., and that of the right pupil, to 1.6 mm.

In both phases anisocoria developed, a divergent type (pseudo-oculomotor phenomenon) being present when the left pupil was large and a convergent type when the left pupil was small.

COMMENT

In view of the results of the pupillographic study, three questions are to be discussed: 1. Is one dealing with a sympathetic spasm traveling over the peripheral sympathetic pathways, thereby actively producing dilation of the pupil, or with a periodic inhibition of the parasympathetic nucleus, with passive production of pupillary dilation by relaxation of the nucleus of the third nerve?

2. Where can the lesion be localized?

3. What conclusions can be drawn as to the role played by the peripheral sympathetic innervation in the pupillary movements in man?

1. *Periodic Sympathetic Spasm Versus Periodic Central Inhibition of Parasympathetic Innervation.*—In an earlier publication, one of us (O. L.), in collaboration with Dr. Isidore Givner,[1] discussed the reasons that, in a case of periodic spasm of the third nerve, we could be sure that the disordered function was indeed due to a spasm produced by the nucleus of that nerve. One of the most important considerations was that synchronously with the contraction of the pupil the ipsilateral levator palpebrae muscle would become activated. In the case now in question, a completely analogous situation was observed in the sympathetically controlled opening of the palpebral fissure, as shown in figure 12. A close relation was seen between the dilation of the pupil and the opening of the palpebral fissure. Whether or not a simultaneous periodic exophthalmos existed or whether intraocular pressure increased or decreased in parallel fashion could not be determined with the technical facilities at our disposal. All sympathetic symptoms other than the opening of the palpebral fissure—in particular, differences in temperature between the right and the left side, loss or diminution of axon reflexes on the left side and the results of mecholyl chloride tests—showed constant (and not periodically developing) functional disturbances.

There was only one periodic phenomenon associated with the periodic sympathetic ocular phenomena, that is, the extension spasm of the wrist and the flexion spasm of the third, fourth and fifth fingers of the left hand; since these spasms appeared each time before the ocular symptoms, which never occurred without being preceded by the movements of the hand, they may be considered to be the stimulus exciting the sympathetic ocular reactions.

The periodic widening of the palpebral fissure is in itself strong evidence for the sympathetic origin of the syndrome, for if it were based on a spasm of the third nerve, one would expect simultaneous pupillary contraction, not the pupillary dilation noted in this case. However, there is other evidence for the spastic sympathetic nature of the phenomenon.

We should first mention that the dilation of the pupil is relatively rapid as compared with the reconstriction, which is very slow and takes approximately six times as long as the dilation. By analogy with other reactions, we may assume that active stimulation produces more rapid effects than relaxation. This statement is not contrary to Sherrington's law that each relaxation of the agonists

produces stimulation of the antagonists. It was seen, for instance, in the case of periodic spasm and relaxation of the third nerve reported by Lowenstein and Givner [1] that the contraction was carried on at almost twice the rate of the relaxation (which produced dilation). If the speed of dilation produced by relaxation of the third nerve is compared with the speed of pupillary dilation in this case, it is found that the average speed of the former was much less (0.33 mm. per second) than that in this case (0.4 mm. per second). On the other hand, the speed of recontraction in our case was 0.07 mm. per second; in the case of active contraction within the oculomotor cycle, however, it was 0.93 mm. per second.

When, in the case of periodic spasm of the third nerve light reflexes were elicited while the automatic dilation was in progress, the speed of this dilation could be decreased to 0.15 mm. per second, i. e., to less than one-half the original

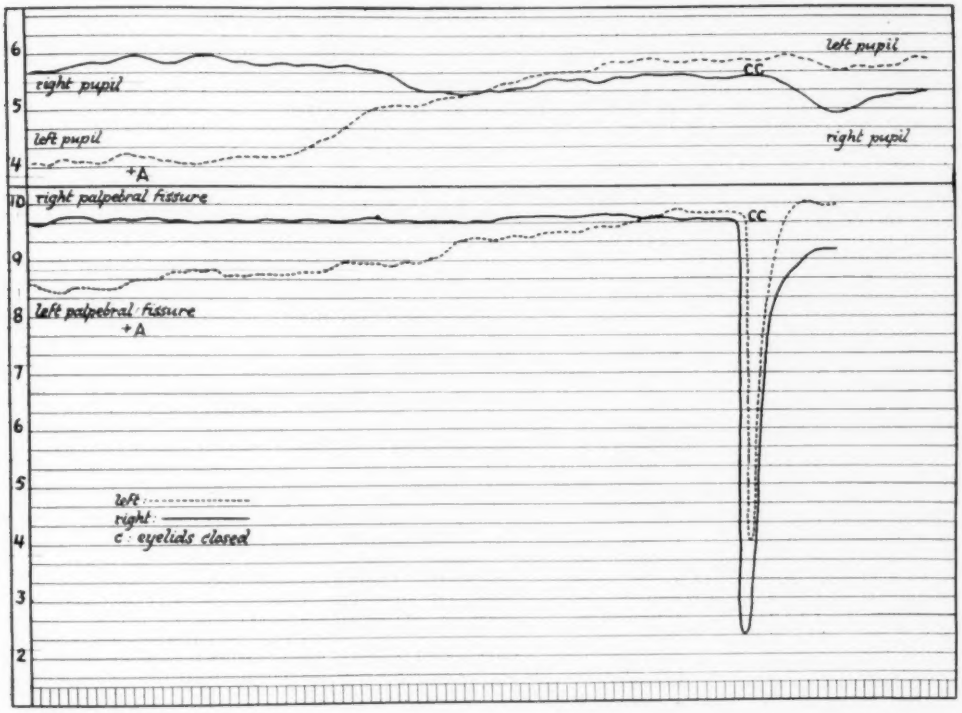

Fig. 12.—Relation of the palpebral fissure to spontaneous movements of the left pupil. When the left pupil becomes large (*A*), a simultaneous enlargement of the left palpebral fissure takes place. Point *cc* indicates the relation of lid closure to the associated pupillary response. The left palpebral fissure was not as completely closed as the right. Likewise, the pupillary contraction on the right side produced by lid closure was more prompt and extensive than that on the left side, while the left pupil was large.

speed; in the present case, however, light reflexes elicited during the phase of dilation of the pupil had no detectable influence on the speed of dilation. Conversely, in the case of oculomotor spasm psychosensory stimulation could not modify the automatic dilation; in the present case, however, such stimulation considerably increased the speed of the dilation. These differences, difficult as they may be to explain in all their details, indicate, nevertheless, that the two processes are undoubtedly different in the 2 cases.

The spastic dilation increased under the influence of cocaine and decreased under the influence of physostigmine. When the left pupil was small, it was

hypersensitive to cocaine and hyposensitive to physostigmine; when large, it was hyposensitive to cocaine and hypersensitive to physostigmine. This fact, too, suggests a sympathetic spasm as the cause of the pupillary dilation.

In line with this argument is the fact that the lid closure reflex, a parasympathetic reflex consisting of pupillary contraction following closure of the lids, was also inhibited during the phase of dilation.

The reaction to near vision caused the disappearance, or at least the diminution, of the anisocoria existing when the pupil was small. This anisocoria, however, was increased at the peak of the contraction when the left pupil was large before the reaction to near vision. This is a phenomenon observed in all cases in which cocaine has caused asymmetric enlargement of the pupil because of decreased sensitivity of one pupil to cocaine. This phenomenon occurs in sympathetic conditions. It is called the pseudo-oculomotor phenomenon (Lowenstein and Franceschetti). The same phenomenon was present in the reactions to light during the periodic phases of active contraction and dilation. It is noteworthy that epinephrine and cocaine produce the phenomenon in the same way.

The psychosensory restitution phenomenon was present to a greater degree in the phase of dilation than in the phase of contraction in the left pupil. This corresponds to the increase in this phenomenon under the influence of cocaine in normal persons, due to increased sensitivity to the liberated epinephrine.

All these facts point to the explanation that the periodic dilation of the pupil is due to an increase in the action of the sympathetic innervation.

2. *Localization of the Lesion.*—The question where the sympathetic system was involved in this case cannot be answered unequivocally. It is probable, however, that the lesion was localized within the first sympathetic neuron, central to the center of Budge.

According to experiments on cats conducted by Hess [5a] and others, a zone for production of mydriasis exists in the posterior hypothalamus and in the region of transition to the midbrain, in an area somewhat lateral to the median line. By stimulation of this region, Hess frequently, although not always, saw simultaneously with pupillary dilation the production of motor symptoms in the lid, bulbus oculi, head and extremities. Since these motor effects were not always, but only frequently, accompanied by the pupillary dilation. Hess assumed that the pupillary reaction was a neighborhood symptom. We therefore suspect that the point of stimulation responsible for the sympathetic phenomenon in the present case was located in the posterior left lateral portion of the hypothalamus, close to the nucleus of the first neuron.

In order to make possible more precise localization of interruptions in the three sympathetic neurons, Foerster and Gagel [6] devised the following scheme:

Drug	Effect on Pupil of Interruption of		
	Third Neuron	Second Neuron	First Neuron
Atropine	+	+	+
Cocaine	—	—	++
Epinephrine	+++	—	—
Pain stimulus	±	±	++

In the present case it may be difficult to make a differential diagnosis on the basis of this scheme because the results obtained when the pupil was considered

5a. Hess, W. R.: Pupille und Zwischenhirn, Klin. Monatsbl. f. Augenh. **103**:407-413, 1939.

6. Foerster, O., and Gagel, O.: Die Vorderseitenstrangdurchschneidung beim Menschen, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:1-92, 1932.

in its large phase differed from those when it was studied in its small phase. We obtained the following results:

Stimulus	Small Pupil	Large Pupil
Atropine	+	+
Cocaine	++	+
Epinephrine	—	—
Pain stimulus	+	—

In the case of the small pupil one would be entitled to localize the lesion in the first neuron, but what about the large pupil, the characteristics of which are not in accordance with the scheme as given?

Foerster's scheme is concerned with interruptions at the different levels of the sympathetic pathways. In the present case, however, the interruptions were certainly not complete, for it was quite evident that the sympathetic innervation was active, although to a lesser degree, when the pupil was small and, to a greater degree, when the pupil was large.

One of us (Lowenstein), on the basis of pupillographic experience with patients and the results of animal experimentation, has endeavored to construct a scheme by which one may distinguish between sympathetic lesions which are irritative, on the one hand, and those which are paretic and paralytic, on the other. This scheme, to be published in full in a later article, is presented here as it applies to sympathetic disturbances, with particular reference to the present case.

	First Neuron		Present Case	
	Irritative	Paretic	Large Pupil	Small Pupil
Atropine	+	+	+	+
Cocaine	+	+	++	++
Epinephrine	—	—	—	—
Sensory stimuli	±	++	—	+
Light reflex	Tonohaptic; pupillotonic absence of reflex	Tonohaptic; complete or incomplete dilation block	Decreased	Tonohaptic
Psychosensory restitution phenomenon	—	++	±	±
Physostigmine	++	++	++	++
Dynamic anisocoria	—	—	—	—
Pseudo-oculomotor phenomenon	+	+	+	+
Near vision	+	+	+	+

If we base the differential diagnosis in our case on this scheme, we find that the small pupil corresponds to a paretic condition of the central sympathetic innervation. The large stage, however, corresponds to an irritative condition of the central sympathetic system. Neither condition is quite pure; the nucleus of the third nerve, too, may be involved. The state of the psychosensory restitution phenomenon indicates the possibility of a lesion in the communications between the hypothalamus and the nucleus of the third nerve (inhibition pathways of the third nerve).

3. *Role of the Sympathetic Innervation in the Pupillary Movements in Man.*—Since the absence or diminution of the psychosensory restitution phenomenon (while the psychosensory dilation phenomenon was present) indicates interruption or lesion of those pathways by which inhibition and desinhibition of the third nerve goes on, we are able to draw conclusions as to the importance of the sympathetic pathways in pupillary control.

Contrary to the opinions expressed in a number of older and recent publications, we found that in the present case, in which the inhibition pathways to the

nucleus of the third nerve were thought to be poor, the sympathetic system stimulated from a point above the center of Budge produced dilation of the pupil consisting of several phases and resulting in total dilation of about 2.05 mm. in about 5.25 seconds, i. e., with an average speed of about 0.4 mm. per second. The reconstriction occurred in about 30 seconds, with an average speed of about 0.07 mm. per second.

When a light reflex was elicited in this case during the phase of active dilation, the contraction resulting was less than that in either the small stage or the stage of complete dilation. The same was true for other parasympathetic reflexes, for instance, the lid closure reflex. On the other hand, if the parasympathetic reflexes, such as the light or the lid closure reflex, were elicited during the period of active contraction following the spastic dilation, these reflexes were increased and were better developed than they were when the pupil was at the peak of dilation or in the corresponding stage of active dilation (i. e., when its diameter was the same) or after its contraction was complete. These facts give evidence for the conclusion, since active dilation inhibits parasympathetic reflexes and relaxation from dilation enhances them, that a real antagonism exists between the sympathetic and the parasympathetic innervation of the pupil.

When a sound stimulus was given during the active phase of dilation, and the patient was startled, a psychosensory dilation effect was added to the spontaneous dilation. When, however, the same was done in the beginning of the period of relaxation, no psychosensory dilation phenomenon could be observed. This means that in the beginning of the period of relaxation (immediately after complete dilation from sympathetic spasm) the sympathetic nerves were apparently paralyzed to some xetent.

The maximal light reaction was obtained during the large phase—not when the dilation had reached its peak but shortly after the peak had been passed. This means, as has been confirmed by other experiments, that a certain well defined degree of sympathetic innervation is necessary in order to permit a maximal light reaction.

Spastic dilation in itself does not produce the so-called spastic mydriatic pupillary immobility, which was not seen in our case. A certain duration, as well as a sufficiently high degree, of spastic dilation is necessary to production of that phenomenon, as in Adie's pupillary syndrome, in which the spastic mydriatic immobility to light may be suppressed by application of physostigmine (Lowenstein).

The light reflex elicited when the sympathetic innervation is in spastic activity and the reflex elicited when it is relaxed show characteristic differences. When the sympathetic innervation is relaxed and the pupil is small, the primary phase of contraction is present, the secondary phase is diminished and the tertiary phase is absent. When the sympathetic innervation is in spastic activity and the pupil is large, the primary phase of contraction is the same as that in the small pupil, but the secondary and tertiary phases are prolonged. This implies that the sympathetic innervation does not influence the entire contraction to light but affects only the secondary and tertiary phases. If the sympathetic innervation is weakened, a decrease in the secondary and tertiary phases of contraction is therefore produced. When these phases of contraction disappear completely, the so-called tonohaptic type of light reaction appears (Lowenstein and Westphal[7]),

7. Lowenstein, O., and Westphal, A.: Experimentelle und klinische Studien zur Physiologie und Pathologie der Pupillenbewegungen mit besonderer Berücksichtigung der Schizophrenie, Berlin, S. Karger, 1933.

which is characteristic of a certain number of disturbances of the central sympathetic system.

Under the influence of cocaine, both spontaneous pupillary phases (small and large) persisted; however, when a light reaction was elicited in the small phase of the cocainized pupil, this contraction showed, unlike the noncocainized small pupil, a secondary and a tertiary phase of contraction. This means that cocaine activates the secondary and tertiary phases of contraction, which is another proof that these phases are of sympathetic origin. In the large phase of the cocainized pupil, all three phases of contraction of the light reflex were diminished. This means that the development of the secondary and tertiary phases is in direct dependence on the functional integrity of the sympathetic innervation. When, however, this functional capacity surpasses a certain level, not only are the secondary and tertiary phases of contraction abolished, but that portion of the contraction controlled by the third nerve is also neutralized, namely, the primary phase. Spastic mydriatic pupillary immobility results, as in Adie's syndrome.

When the pupil was contracted with physostigmine, both stages produced by spontaneous sympathetic activity persisted. The light reaction in the small physostigminized pupil was sluggish, consisting almost solely of a slow primary contraction. Sympathetic activity, as shown in the large pupillary phase, produced an increase in the primary phase of contraction to light but was not sufficient to produce a secondary and a tertiary phase. This means that the primary phase of contraction, which is enhanced by the sympathetic activity, is an expression of activity of the third nerve, facilitated by neutralization of a certain amount of acetylcholine by the epinephrine elaborated by the sympathetic innervation.

Tonohaptic reactions appear as fatigue symptoms more often when the pupil is small than when it is large, an indication that inactivity of the sympathetic innervation facilitates the oncoming symptoms of fatigue. The first symptoms of fatigue within the light reaction were in this case characterized by disappearance of the secondary and tertiary reaction phases. In cases in which the nucleus of the third nerve is damaged, without superimposed lesion of the sympathetic pathways, the first symptoms of fatigue to appear consist of an initial dilation preceding the contraction.

CONCLUSIONS

A syndrome of periodic sympathetic spasm and subsequent relaxation occurred in a woman aged 22. This patient suffered from a progressive degenerative condition of the central nervous system, characterized by gradual development of motor and sensory disturbances, peculiar gait and periodic spastic extension at the wrist and flexion of the ulnar three fingers, which preceded by some seconds the periodic pupillary phenomena. A number of other sympathetic and parasympathetic symptoms were noted.

Impulses traveling over the sympathetic pathways produce a pupillary dilation consisting of several dilation phases at an average speed of 0.4 mm. per second, which in this case was 2 mm., followed by contraction at an average speed of about 0.07 mm. per second.

The light reflex of the pupil, usually considered to be a parasympathetic reflex, contains in its phase of contraction some factors, particularly the secondary and tertiary phases, which are determined by the functional state of the sympathetic system, whereas the primary phase of contraction depends predominantly on the parasympathetic system.

A certain functional sympathetic tonus is necessary in order that a maximal sympathetic reaction, for example, a maximal psychodilation reflex, may be guaranteed.

A certain, well defined degree of sympathetic innervation is necessary for a maximal parasympathetic reaction, such as the light reflex.

When the secondary and tertiary phases in the contraction of the light reflex are poor, cocaine will improve them.

The primary phase of contraction of the light reflex is the expression proper of the influence of the third cranial nerve. When the pupil is contracted with physostigmine and the primary phase of contraction of the light reflex is poor, it can be improved by the occurrence of spontaneous sympathetic spasm, as a result of the neutralization of physostigmine by the liberated epinephrine.

Poor sympathetic innervation facilitates the occurrence of symptoms of fatigue within the pupillary light reflex, characterized by early disappearance of the secondary and tertiary phases of contraction. There exists another type of fatigue, however, due to damage to the nucleus of the third nerve, which is manifested first as an initial dilatation preceding the contraction to light.

Fatigue of the sympathetic type, due to poor sympathetic innervation, frequently appears in the form of tonohaptic reactions, characterized by loss of the secondary and tertiary phases of contraction.

When the pupil becomes small because of poor sympathetic innervation, hypersensitivity to cocaine and hyposensitivity to physostigmine develops. Conversely, when the pupil becomes large under the influence of hyperinnervation by the sympathetic system, hypersensitivity to physostigmine and hyposensitivity to cocaine develop.

Differentiation of the three phases of contraction by analysis of the light reflex makes it possible to eliminate either the parasympathetic or the sympathetic factor, so that their respective strengths may be evaluated.

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Clinical Notes

A VACUUM DEVICE FOR THE EYELIDS

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The expression of the meibomian glands by digital pressure or by some form of spatula, while not very painful, is occasionally objected to by the patient. A few weeks ago, in a situation of this kind, I attached the glass portion of a medicine dropper to the tubing of the suction apparatus I use for nasal displacement treatment. I found that passage of the end of the dropper back and forth along the margin of the lids tended to evacuate concretions from both the meibomian glands and the hair follicles.

The degree of vacuum does not have to be regulated. The end of the dropper is so small that the tube usually collapses and no trauma is produced. If the end happens to slip on to the bulbar conjunctiva, one can immediately stop the pressure by pinching firmly the connecting rubber tubing and then slowly and gently release the point.

Experience with this method has shown that occasionally an eye dropper has an end of greater caliber than usual and is then too large. A dropper with a medium or small end is necessary.

I have found this procedure a valuable adjuvant to treatment in practically all my cases of chronic and in some cases of acute conjunctivitis. I instil a drop of 0.5 per cent solution of pontocaine hydrochloride a minute before I use the suction and 2 drops of a 1 : 500 solution of silver nitrate afterward to take care of any floating material resulting from the suction. This weak solution of silver nitrate does not have to be neutralized. This method of treatment, with the use of sulfathiazole in accordance with Thygeson's [1] directions, gives a much happier outlook in cases of conjunctivitis than has previously been possible.

Some chronic inflammations take a long time to clear up. In selected cases I provide the patient with a piece of rubber tubing attached to the dropper, and he himself, by using mouth suction, can daily evacuate the concretions.

1. Thygeson, P.: Sulfonamide Compounds in Treatment of Ocular Infections, Arch. Ophth. **29**:1000 (June) 1943.

Ophthalmologic Reviews

EDITED BY DR. FRANCIS HEED ADLER

DIABETIC RETINOPATHY

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PHILADELPHIA

Although all ophthalmologists recognize the typical ophthalmoscopic appearance of diabetic retinopathy, first described by Jaeger [1] in 1856, not all are convinced that the fundic picture is specific. There have been many papers in past years that supported each side of the question.[2] Practically all discussions have been based on observations on patients. The facts that diabetic retinopathy is usually associated with retinal arteriosclerosis, hypertension and renal disease and that young persons with diabetes were formerly thought to be free of the retinopathy have led many observers to conclude that diabetic retinopathy is not specific.[3] On the other hand, recent studies have shown that sclerosis of the retinal vessels is not more frequent in diabetic than in nondiabetic patients of a similar age group.[4] Diabetic retinopathy does occur in young persons if observations are made over a sufficiently long time,[5] and this fundic picture does occur in persons free from hypertension, sclerosis of the retinal vessels and renal disease.[6] Attempts have been made to fit all this evidence into one picture and to find a common denominator—one basic pathologic change common to all cases of diabetic retinopathy. This factor should be one that increases in severity with the duration of the disease, for it is well established that the incidence of retinopathy increases with the length of the diabetic state.[7]

HYPERGLYCEMIA

Since hyperglycemia is a metabolic fault in every case of diabetic retinopathy, Elwyn,[8] and recently Duggan,[9] suggested it as the fundamental cause. In doing so, however, they neglected the considerable evidence of Waite and Beetham,[2i] Arruga,[10] Hanum [11] and others, who demonstrated that diabetic retinopathy is most frequent, not in patients with a very high sugar content of the blood but in those with mild hyperglycemia. Duggan [9] suggested that uncontrolled hyperglycemia prior to the administration of insulin was responsible. He expressed the belief that diabetic retinopathy is essentially a capillary disease. The temporary hypoglycemia produced by insulin calls forth epinephrine, with production of arteriolar constriction, which, in turn, is responsible for capillary anoxia, dilatation and increased permeability. Duggan cited cases of other investigators and his own as instances in which improvement occurred with employment of vasodilator drugs.

From the Department of Ophthalmology, Hospital of the University of Pennsylvania.

1. Jaeger, E.: Beiträge zur Pathologie des Auges, Vienna, 1856.

2. (*a*) Friedenwald, J. S.: Symposium on Diabetic Retinitis, Am. J. Ophth. **8**:61, 1925. (*b*) Gradle, H.: Ocular Conditions in Diabetes, ibid. **10**:54, 1927. (*c*) Cohen, M.: The Eye in Diabetes Mellitus, Arch. Ophth. **2**:530 (Nov.) 1929. (*d*) Cammidge, P. J.: Retinitis in Diabetics, Proc. Roy. Soc. Med. (Sect. Ophth.) **23**:24, 1930. (*e*) Dirion, J. K.: Diabetic Retinitis, Arch. Ophth. **9**:829 (May) 1933. (*f*) Wagener, H. P.; Dry, T. J., and Wilder, R. M.: Retinitis in Diabetes, New England J. Med. **211**:1131, 1934. (*g*) Cohen, M.: Lesions of the Fundus in Essential Hypertension and in Arterial and Renal Diseases, Arch. Ophth. **17**:994 (June) 1937. (*h*) Braun, R.: Diabetic Retinitis: A Study of One Hundred and Fifteen Cases, Arch. f. Ophth. **136**:256, 1936; abstracted, Arch. Ophth. **18**: 167 (July) 1937. (*i*) Waite, J. H., and Beetham, W. P.: Visual Mechanism in Diabetes Mellitus, New England J. Med. **212**:367 and 429, 1935. (*j*) Lee, R. H.: The Ocular Fundus in Diabetes Mellitus, Arch. Ophth. **26**:181 (Aug.) 1941. (*k*) Jaeger.[1]

3. Friedenwald.[2a] Gradle.[2b] Cohen.[2c] Cammidge.[2d] Dirion.[2e] Cohen.[2g] Lee[2j]

4. Wagener, Dry and Wilder.[2f] Waite and Beetham.[2i]

5. (*a*) Barkan, H., and Gray, H.: Diabetes and Retinitis, Tr. Am. Ophth. Soc. **35**:80, 1935. (*b*) O'Brien, C. S., and Allen, J. H.: Ocular Changes in Young Diabetic Patients, J. A. M. A. **120**:190 (Sept. 19) 1942.

6. Gresser, E. B.: Studies of Retinopathies: Diabetes Mellitus, Am. J. Ophth. **16**:612, 1933. Wagener, Dry and Wilder.[2f] Waite and Beetham.[2i] Barkan and Gray.[5a]

7. Waite and Beetham.[2i] Barkan and Gray.[5a]

8. Elwyn, H.: Problem of Diabetic Retinitis, Arch. Ophth. **25**:139 (Jan.) 1941.

9. Duggan, W. F.: Clinical Vascular Physiology of the Eye, Am. J. Ophth. **26**:354, 1943.

10. Arruga, H.: Ocular Diabetes, Arch. de oftal. hispano-am. **33**:356, 1932; abstracted, Arch. Ophth. **9**:286 (Feb.) 1933.

11. Hanum, S.: Diabetic Retinitis, Acta ophth., 1939, supp. 16, p. 3; abstracted, Am. J. Ophth. **22**:804, 1939.

VASCULAR STATUS

Cohen [12] insisted that sclerosis of the retinal vessels, though not always seen ophthalmoscopically, was probably always present histologically and was the cause of the retinopathy. This hypothesis may be correct, but his pathologic evidence was based on too few cases and did not exclude hypertension as a factor. Cohen received considerable support in this belief. Friedenwald [13] classified diabetic retinopathy as a particular type of arteriosclerosis of the retina. It has been shown that as the severity of sclerosis of retinal vessels increased the incidence of diabetic retinopathy rose.[14] These observations favor an arteriosclerotic origin, but it is also known that arteriosclerosis alone rarely produces retinal changes identical with those of diabetes.[15]

In past analyses, sufficient attention has not been paid to the type of sclerosis encountered in the retinal vessels. One must differentiate atherosclerosis, arteriolar sclerosis, Mönckeberg's sclerosis and senile arteriosclerosis [16] before much significance can be attached to the incidence of the sclerosis. It is true that Mönckeberg's type rarely, if ever, occurs in retinal vessels, but the other forms may cause recognizable changes in these vessels.[17] All these types of sclerosis have been loosely referred to as arteriosclerosis.

There is considerable evidence that, of the types of sclerosis, only atherosclerosis is more frequent in the diabetic than in the nondiabetic patient of the same age group.[18] A few investigators are not convinced that even atherosclerosis is more frequent or that there is any cause and effect relation between diabetes mellitus and atherosclerosis.[19] Atherosclerosis of the retinal vascular tree has been pathologically demonstrated to exist, chiefly in the central retinal artery,[17a] and there are no available data to show that atherosclerosis is either more or less frequent in the central retinal artery of the diabetic person. The data of Bridgett [20] indicate that the presence or absence of atherosclerosis elsewhere in the body cannot be used as evidence for or against the existence of atherosclerosis of the central retinal artery.

Duke-Elder [21] stated that involutional arteriosclerosis, which he asserted is synonymous with diffuse atherosclerosis, and which corresponds to the senile arteriosclerosis of Wilder, Joslin and others, is of greater incidence and severity in the fundus of the diabetic person than in that of the nondiabetic person. The majority of data indicate that sclerosis of vessels elsewhere in the body the size and caliber of retinal vessels is not increased in the diabetic patient,[22] and Wagener, Dry and Wilder [2f] and Waite and Beetham [21] were unable to demonstrate any increase in sclerosis in the retinal vessels of diabetic patients as compared with those of nondiabetic persons of the same age group.

Recently Wagener and associates,[2f] O'Brien and Allen,[23] Gibson and Smith,[24] Ballantyne [25] and Michaelson and Campbell,[26] as well as others, have directed attention to the venous system of the retina as playing a significant role in pathologic changes in the fundus associated with diabetes. Ballantyne [25] expressed the belief that fulness of the retinal veins is one of the earliest changes in the retina in diabetes mellitus. However, he was unable to explain the cause of this fulness. He suggested a slight obstruction of the central retinal vein and, as evidence of this, presented 16 cases of occlusion of the central vein, in 15 of which the condition

12. Cohen.[2e, g]

13. Friedenwald, J. S.: The Pathology of the Eye, New York, The Macmillan Company, 1929.

14. Leopold, I. H.: Ocular Findings in Ten Year Treated Diabetes Mellitus, Arch. Ophth. **27**:422 (Feb.) 1942. Waite and Beetham.[21]

15. Lee.[2j] Barkan and Gray.[5a]

16. (*a*) Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1940, p. 423. (*b*) Wilder, R. M.: Clinical Diabetes Mellitus and Hyperinsulinism, Philadelphia, W. B. Saunders Company, 1940, p. 275.

17. (*a*) Friedenwald, H.: The Pathological Changes in the Retinal Blood Vessels in Arteriosclerosis and Hypertension (Doyne Memorial Lecture), Tr. Ophth. Soc. U. Kingdom **50**:452, 1930. (*b*) Ballantyne, A. J.: The Evolution of Retinal Vascular Disease, ibid. **57**: 301, 1937.

18. Joslin, Root, White and Marble,[16a] pp. 424-426. Wilder,[16b] pp. 329-333.

19. (*a*) Lavietes, P. H.: Blood Sugar as a Criterion of Therapy: The Use of Insulin and Protamine Insulin in Treatment of Diabetes, in Steele, J. M., and others: Advances in Internal Medicine, New York, Interscience Publishers, Inc., 1942, vol. 1, p. 41. (*b*) Tolstoi, E., in Conferences on Therapy: Management of Diabetic Emergencies; Treatment of Surgical Patients, J. A. M. A. **115**:529 (Aug. 17) 1940.

20. Bridgett, C. R.: Sclerosis of the Central Artery of Retina, Am. J. Ophth. **9**:725, 1926.

21. Duke-Elder, S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 2732.

22. Joslin, Root, White and Marble,[16a] p. 424. Wilder,[16b] pp. 329-330.

23. O'Brien, C. S., and Allen, J. H.: Unusual Changes in Retinal Veins in Diabetes, Tr. Sect. Ophth., A. M. A., 1940, p. 148.

24. Gibson, G. G., and Smith, L. W.: Retinal Phlebosclerosis, Tr. Sect. Ophth., A. M. A., 1941, p. 58.

25. Ballantyne, A. J.: Recent Work on Vascular Disease and Its Significance in Medical Ophthalmology, Glasgow M. J. **138**:1, 1942.

26. Michaelson, I. C., and Campbell, A. C. P.: Anatomy of the Finer Retinal Vessels and Some Observations on Their Significance in Certain Retinal Diseases, Tr. Ophth. Soc. U. Kingdom **60**:71, 1940.

was associated with diabetes. Michaelson and Campbell,[26] working with carefully prepared retinal tissue, indicated that the deep retinal capillary plexus is more closely knit than the superficial capillary plexus, and they therefore concluded that the circulation tends to be relatively more sluggish here, even under normal conditions. These authors noticed in retinal tissue of diabetic patients dilatation of the veins of the third order of division. This dilatation would produce congestion, which would be felt in the capillary system. Since the deep plexus is more dependent than the superficial plexus, the meshwork closer and the circulation slower, the back pressure is more felt there, and blood passes from these vessels into the outer molecular layer, with production of punctate hemorrhages. This theory is a plausible one. However, these observers failed to state the number of cases in which such a pathologic state was observed. Others, namely, Mylius,[27] Elwyn [8] and Ricker,[28] have postulated a similar theory.

Agatston,[29] in a careful pathologic study now under way, noted sclerotic lesions of the veins, which extended to involve the venules and the capillaries. He noted fibrosis of the retinal vessels, hyalinization of the walls and separation of the longitudinally directed fibrils. These changes, although also present in the retina of nonhypertensive and hypertensive patients, were more frequent and severe in diabetic patients. He observed that the capillaries in the internal nuclear layer were most involved. It remains to be seen whether such changes are to be seen in all persons with diabetic retinopathy. Beauvieux and Pesme [30] reported sclerosis and hyalinization of venous walls, while Gibson and Smith [24] noted sclerotic changes in the veins in only 2 of 8 patients with diabetic retinopathy on pathologic examination.

O'Brien and Allen [23] and Gibson and Smith [24] gave good descriptions of venous changes in diabetic persons but were careful to note that such lesions were not always present. The incidence of varices of the retinal veins, for example, in patients with diabetic retinopathy is about 1 per cent. Wagener,[31] who had had wide experience with persons with diabetes mellitus, expressed the opinion that venous changes in the retina are not sufficiently severe or characteristic to account for the changes in diabetic retinopathy, although earlier he had postulated such a theory.[2f]

27. Mylius, C.: Ueber Retinitis Diabetica, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **51**:150, 1936.

28. Ricker, G.: Pathologie als Naturwissenschaft, Berlin, Julius Springer, 1924.

29. Agatston, S. A.: Clinicopathologic Study of Diabetic Retinitis, Arch. Ophth. **24**:252 (Aug.) 1940.

30. Beauvieux and Pesme, P.: Rétinite diabétique, Arch. d'opht. **40**:65, 1923.

31. Wagener, H. P., in discussion on Gibson and Smith.[24]

STATUS OF VITAMIN THERAPY

Friedenwald [32] reported that patients with diabetic retinopathy showed an increased capillary fragility, as indicated by petechial hemorrhages in the skin after standard suction was applied. He claimed that the fragility returned to normal when ascorbic acid and vitamin B complex were given. Later investigators, including Friedenwald himself, failed to confirm these results. However, Yudkin [33] reported benefit from the use of 4 or 5 ounces (120 or 150 cc.) of lemon juice daily, particularly when the pulp was included. Rusznyák and Szent-Györgyi [34] and others [35] expressed the belief that citrin, or vitamin P, is the antifragility factor and that this factor, present in fruit juices, pulp and skin, is absent from synthetic vitamin C. Other observers are still not convinced as to its merits. Although Burch [36] reported benefit from the use of vitamin K in cases of hemorrhagic retinitis, it is well known that this vitamin is effective only in cases in which the prothrombin time is increased. It is not likely that the prothrombin time is increased in all cases of diabetic retinopathy, but no evidence is available to justify any conclusion.

It has been shown that vitamin A deficiency can arise in persons with pancreatic dysfunction, especially with prolonged faulty fat metabolism.[37] Carbohydrate metabolism is deranged in persons with vitamin B avitaminosis.[38] Vitamin C reduces the level of the blood sugar in

32. Friedenwald, J., cited by Gifford, S. R.: Ocular Therapeutics, ed. 3, Philadelphia, Lea & Febiger, 1942, p. 85.

33. Yudkin, A. M.: Vitamins in Treatment and Prevention of Ocular Diseases, Arch. Ophth. **19**:366 (March) 1938.

34. Rusznyák, S., and Szent-Györgyi, A.: Vitamin P, Nature, London **140**:426, 1937.

35. Scarborough, H., and Stewart, C. P.: Effect of Hesperidin on Capillary Fragility, Lancet **2**:110, 1938. Ivy, A. C., and Gray, J. S.: Vitamin P and Capillary Fragility, Internat. Abstr. Surg. **69**:4, 1939; in Surg., Gynec. & Obst., July 1939.

36. Burch, E. P.: Treatment of Hemorrhagic Retinitis with Vitamin K, Minnesota Med. **22**:32, 1939.

37. Wirtshafter, Z. T., and Korenberg, M.: Diabetes Mellitus, Baltimore, Williams & Wilkins Company, 1942, p. 62.

38. Williams, R. R.: The Chemistry and Biological Significance of Thiamin, Science **87**:559, 1938.

patients with diabetes mellitus and does not affect the blood sugar in normal persons.[39] However, there has not been sufficient evidence to show that avitaminosis is the root of evil in diabetic retinopathy.

ENDOCRINE GLANDS

Much experimental work has been done to demonstrate the role of the endocrine glands in diabetes mellitus. Reduced sugar tolerance occurs in patients with acromegaly[40] and basophilic adenoma.[41] Diabetic retinopathy may accompany both these pituitary disturbances. It is known that removal of the anterior lobe of the pituitary causes a low sugar content of the blood, increased sensitivity to insulin and decreased breakdown of protein.[37] The pancreatic secretion tends to preserve the depots of foodstuffs in various parts of the body, while the pituitary hormone tends to mobilize these depots.[42]

Thyroxin increases the carbohydrate oxidation of the body tissues,[43] while epinephrine can effect mobilization of the sugar in the blood. Lack of adrenal cortical hormone can result in amelioration of pancreatic diabetes in dogs and of diabetes in man[44]; also, an adrenalectomized animal suffers from inability to mobilize fat from the depots and to transport it to the liver.[45] Estrogen reduces the amount of insulin required.[46] At present there is insufficient evidence that any of the endocrine glands play a direct role in causing diabetic retinopathy, although, through their influence on the level of sugar in the blood, fat metabolism and sensitivity to insulin, they may play a role.

CHEMICAL CONSTITUENTS OF THE BLOOD

Waite and Beetham[21] and Hanum,[11] in studies on the influence of chemical constituents of the blood other than sugar, were unable to attach any importance to urea, uric acid or creatinine. Cammidge[2d] insisted that calcium played a role, but other investigators failed to confirm his observations.[47]

FAT METABOLISM

For years attention has been paid to fat metabolism in diabetes mellitus. It is now known, largely through the work of Stadie,[48] that when fats are burned to limits of the body's capacity, the excess has to be excreted in the urine and that its accumulation in the tissues is favored. Experimentally it has been shown that depancreatized animals maintained on a regulated diet and insulin still show depositions of lipids in their livers.[49] Lecithin,[50] choline,[51] autoclaved pancreas[52] and lipocaic[53] were found effective in preventing deposition of excessive amounts of lipids in the livers of depancreatized dogs. Dragstedt[53] indicated a parallelism between the development of fat in the liver and arteriosclerosis in dogs deprived of lipocaic. It has been pointed out that with fatty infiltration of the liver the diabetic patient may show an increasing tolerance for carbohydrates and present no signs of poor control.[54] So it is possible, and likely, that subendothelial deposition of fat associated with atherosclerosis occurs in all patients with diabetes, whether controlled or not.

39. Pfieger, R., and Scholl, F.: Diabetes und Vitamin C, Wien. Arch. f. inn. Med. **31**:219, 1937.

40. Cushing, H., and Davidoff, L. M.: The Pathological Findings in Four Autopsied Cases of Acromegaly, Monograph 22, Rockefeller Institute for Medical Research, 1927, p. 131.

41. Cushing, H.: Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations, Bull. Johns Hopkins Hosp. **50**:137, 1932.

42. Long, C. N. H., and Lukens, F. D. W.: Observations on Dog Maintained for Five Weeks Without Adrenals or Pancreas, Proc. Soc. Exper. Biol. & Med. **32**:392, 1934.

43. Foster, D. P., and Lowrie, W. L.: Diabetes Mellitus Associated with Hyperthyroidism, Endocrinology **23**:681, 1938.

44. Long, C. N. H.; Katzin, B., and Fry, E. G.: The Adrenal Cortex and Carbohydrate Metabolism, Endocrinology **26**:309, 1940.

45. Barnes, R. H.; Miller, E. J., and Burr, G. O.: The Effect of Adrenalectomy on the Deposition in the Liver of Spectroscopically Active Fatty Acids, J. Biol. Chem. **140**:241, 1941.

46. Spiegelman, A. R.: Influence of Estrogen on Insulin Requirements of the Diabetic, Proc. Soc. Exper. Biol. & Med. **43**:307, 1940.

47. Lawrence, R. D.; Millar, H. R., and Madders, K.: Blood Calcium in Diabetic Retinitis, Brit. M. J. **2**:559, 1930. Quick, A. J.: A Classification of Hemorrhagic Diseases Due to Defects in the Coagulation Mechanism of the Blood, Am. J. M. Sc. **199**:118, 1940. Waite and Beetham.[21]

48. Stadie, W. C.: Fat Metabolism in Diabetes Mellitus, J. Clin. Investigation **19**:843, 1940.

49. Chaikoff, I. L., and Kaplan, A.: The Blood Lipids in Completely Depancreatized Dogs Maintained with Insulin, J. Biol. Chem. **106**:267, 1934; Liver Lipids in Completely Depancreatized Dogs Maintained with Insulin, ibid. **108**:201, 1935.

50. Hershey, J. M.: Substitution of Lecithin for Raw Pancreas in the Diet of the Depancreatized Dog, Am. J. Physiol. **93**:657, 1930. Hershey, J. M., and Soskin, S.: Substitution of Lecithin for Raw Pancreas in the Diet of the Depancreatized Dog, ibid. **98**:74, 1931.

51. Best, C. H.; Ferguson, G. C., and Hershey, J. M.: Choline and Liver Fat in Diabetic Dogs, J. Physiol. **79**:94, 1933.

52. Kaplan, A., and Chaikoff, I. L.: Effect of Autoclaved Pancreas upon Lipids of Blood and Liver in Depancreatized Dogs Maintained with Insulin, Proc. Soc. Exper. Biol. & Med. **34**:606, 1936.

53. Dragstedt, L. R.: Present Status of Lipocaic, J. A. M. A. **114**:29 (Jan. 6) 1940.

54. Anderson, G. E.: Problem of Retinitis in the Diabetic Patient, Arch. Ophth. **28**:679 (Oct.) 1942.

It may be that the use of lipocaic or some other insulin-free pancreatic extract may prevent this deposition of fats in vessels, as well as in the liver. The clinical status of these lipotropic agents is unsettled at present.[55]

For one to attach any therapeutic importance to lipotropic agents in the control of sclerosis in cases of diabetes, it is necessary to believe that it is atherosclerosis that is increased in incidence in the diabetic patient and that atherosclerosis is initiated by deposition of fat in the vessel walls. The experiments of Aschoff[56] and Leary[57] favor the theory of deposition of fat in vessel walls as the cause of atherosclerosis. The experiments of Duff[58] and others do not.[59] Although it has been shown that the incidence of diabetic retinopathy increases with increasing ophthalmoscopically recognizable sclerosis of retinal vessels,[60] one must remember that there exists no pathologic proof of increase in atherosclerosis of the central retinal artery associated with diabetes mellitus. So it is clear that the value of a lipotropic agent in prevention of diabetic retinopathy is at best largely theoretic and uncertain.

Hyperlipemia, measured by the level of cholesterol, is often elevated in cases of diabetes mellitus. In the majority of such cases the hyperlipemia is based on dehydration and hemoconcentration.[19a] It disappears when glycosuria is controlled, even though the hyperglycemia persists.[61]

Peters[62] studied the small group of cases with persistently high lipid levels of the blood even when glycosuria and fluid balance are controlled, and showed that the hyperlipemia in these cases is probably based on coincidental lesions, and not on the diabetes mellitus itself.

Experimental studies indicate that hypercholesteremia alone is not capable of producing retinal changes, but that when it is combined with local injury deposits of cholesterol in the retina may result.[63] It may well be that once vascular disease, a form of local injury, appears, the surrounding tissues become more susceptible to possible damage from hyperlipemia. Perhaps lipotropic agents may be helpful here.

It is evident that in attempting to treat diabetic retinopathy one must attack several enemies, not knowing which one is doing the real damage, or even that one is cognizant of all the possible culprits.

TREATMENT

Anderson[54] has recently reviewed the subject of fat metabolism in diabetes mellitus and has suggested three major aims for therapy. These aims are accepted by many metabolic clinicians. The patient should receive a high carbohydrate diet in order that mobilization of fat may be kept to a minimum. The patient should receive sufficient protein, on the basis of work which has demonstrated the protective value of animal protein in preventing accumulation of fat in the liver and degeneration of the liver.[64] Since Dragstedt[53] has shown a parallelism between the development of a fatty liver and arteriosclerosis in dogs, protein may also protect the vessels against deposition of lipids. The caloric intake and the blood sugar should be kept at a level which does not permit the patient (if an adult) to gain or lose weight or allow glycosuria to occur. Many clinicians feel it is safer to permit a trace of sugar in the urine than to subject the patient to the dangers of hypoglycemia, such as may result in angina pectoris and occlusion of the coronary arteries in susceptible persons. Lukens[65] suggested that in any case determination of the cholesterol content of the serum two or three times a year will be of some help in recording of the control of fat metabolism. If more knowledge of the endocrine control of fat metabolism is acquired, it should be useful. At present, administration of thyroid is the only obvious means of lowering the cholesterol content of the blood, and this only in certain states and when carried out with due care. One

55. Klein, C.; Saland, G., and Zurrow, H.: Pancreatic Tissue Extract (Insulin-Free) in the Treatment of Peripheral Vascular Disease, Ann. Int. Med. **18**:214, 1943. Wolffe, J.: Pancreatic Extract, Am. J. Surg. **43**:109, 1939.

56. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, 1924.

57. Leary, T.: Experimental Atherosclerosis in Rabbit Compared with Human (Coronary) Atherosclerosis, Arch. Path. **17**:453 (April) 1934.

58. Duff, G. L.: Experimental Cholesterol Arteriosclerosis and Its Relationship to Human Arteriosclerosis, Arch. Path. **20**:81 (July); 259 (Aug.) 1935.

59. Weiss, S., and Minot, G. R.: Nutrition in Relation to Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis: A Survey of the Problem, New York, The Macmillan Company, 1933, p. 233. Watson, E. M., and Wharton, M. A.: A Comparison of Various Diets in the Treatment of Diabetes Mellitus, Quart. J. Med. **4**:277, 1935.

60. Waite and Beetham.[21] Leopold.[14]

61. Chaikoff, I. L.; Smyth, F. S., and Gibbs, G. E.: The Blood Lipids of Diabetic Children, J. Clin. Investigation **15**:627, 1936.

62. Peters, J. P., and Man, E. B.: Serum Lipoids in Diabetes, J. Clin. Investigation **14**:579, 1935.

63. Jess, 1925, cited by Friedenwald.[13] Sugita, 1923, cited by Friedenwald.[13]

64. Goldschmidt, S.; Vars, H. M., and Ravdin, I. S.: The Influence of Foodstuffs upon the Susceptibility of the Liver to Injury by Chloroform and the Probable Mechanism of Their Action, J. Clin. Investigation **18**: 277, 1939.

65. Lukens: Personal communication to the author.

must be certain that ample vitamins are included in the diet. In completion of the diet, fluid balance should be well maintained because, as noted, in many cases hyperlipemia really develops on a basis of dehydration.

Since it is known that the presence of hypertension and renal disease unfavorably influences the incidence of diabetic retinopathy,[7] careful attention must be directed to the avoidance of these conditions. A rise in blood pressure tends to produce hemorrhage in already damaged vessels, or may damage vessels, which hyperlipemia may enhance. A fall in blood pressure may induce harmful ischemia in a patient already adjusted to a high blood pressure. In the presence of renal disease, the acid-base balance must be controlled so that no extra burden of excretion is thrown on the kidneys, and elimination by other routes should be aided.

Duke-Elder [66] stressed the importance of control of sepsis, especially in an effort to reduce the incidence of massive retinal hemorrhages. Richardson,[67] in an attempt to evaluate the influence of diabetes on the antibacterial property of blood, showed that the diabetic patients who were in the most unsatisfactory metabolic balance, formed the smallest amount of agglutinin titer against a specific amount of antigen, such as typhoid vaccine. This, also, should impress one with the importance of prevention of infection, as well as control of the diabetes.

66. Duke-Elder,[21] p. 2733.

67. Richardson, R.: Immunity in Diabetes, J. Clin. Investigation **19**:239, 1940.

PROGNOSIS

Bardsley,[68] Folk and Soskin [69] and recently O'Brien and Allen [5b] and Duggan [9] described cases in which benefit was obtained from therapy. Observations on 100 diabetic patients who had been well treated and who had cooperated well in their therapy for over ten years revealed that no great influence on the incidence and course of diabetic retinopathy could be expected from such treatment.[14]

At present, hyperglycemia, excess deposition of fat, vascular sclerosis and changes in the capillaries and, particularly, in the veins are considered probable causative factors in diabetic retinopathy. Disturbances in chemical constituents of the blood, vitamin deficiencies and endocrine disorders must also be reckoned with. Therapy is largely directed against these possibilities, even though usually such a regimen will not promise the patient prevention or regression.

3400 Spruce Street.

68. Bardsley, in Round Table Discussion on Diabetes Mellitus, Tr. Ophth. Soc. U. Kingdom **40**:43, 1920.

69. Folk, M. L., and Soskin, S.: The Fundus Oculi in Diabetes Mellitus, Am. J. Ophth. **8**:432, 1935.

News and Notes

EDITED BY DR. W. L. BENEDICT

SOCIETY NEWS

Pan-American Congress of Ophthalmology.—The Uruguayan committee in charge of the organization of the Second Pan-American Congress of Ophthalmology, which was to be held in Montevideo, Uruguay, in 1943, resolved to postpone this congress until 1944. The exact date will be announced later. The scientific program as it has been published in previous announcements remains unmodified. It is as follows: The first day will be given to a consideration of social ophthalmology, the morning session to cover "Prevention of Blindness in the Americas" and the afternoon session, "The Status of Trachoma in the Americas." The second day will be devoted to research in ophthalmology, eight studies to be selected by the committee on arrangements. The third day will be given to a consideration of glaucoma, the topics to be "The Preglaucomatous State—Its Diagnosis and Treatment," "New Ideas on Glaucoma Derived from Gonioscopy," "Estimation and Mechanism of the Destructive Effects of Ocular Hypertension" and "Surgical Intervention in Glaucoma and How Far Medical Treatment Can Be Continued." The fourth day will be dedicated to a consideration of the surgical therapy of paralytic strabismus, heterophoria and concomitant strabismus, and the fifth day, to free discussion of topics selected by the congressists.

Association for Research in Ophthalmology.—A meeting of the Association for Research in Ophthalmology will be held June 13, 1944 at the Hotel Sherman, Chicago. Applications for places on the program are being received, and all communications should be mailed to the secretary, Major Brittain F. Payne, School of Aviation Medicine, Randolph Field, Texas.

UNIVERSITY NEWS

University of Kansas School of Medicine.—Dr. E. J. Curran, Kansas City, Mo., has contributed $10,000 to the University of Kansas School of Medicine for equipment, material and assistance for research in the department of ophthalmology of the medical school.

SPECIAL NEWS

Benjamin Franklin Bifocal Glasses.—The National Franklin Committee, organized by the Franklin Institute, in Philadelphia, in referring to Benjamin Franklin's contributions to medical science, speaks of the discovery of bifocal glasses and quotes the original words:

"Before that year [1784], I had used two pair of spectacles which I shifted occasionally, as in travelling I sometimes read and often wanted to regard the scenery. Finding this change troublesome and not always sufficiently ready, I had the glasses cut and half of each kind (of lens) associated in the same circle."

Correspondence

OPERATIVE TREATMENT OF SQUINT

To the Editor.—I have just read the interesting article by Major H. Saul Sugar in the November 1943 issue of the ARCHIVES which concerns the operative treatment of squint. This study parallels one which I had been carrying on for two years or more at the Brooklyn Eye and Ear Hospital but which, unfortunately, was interrupted by my entry into active military service.

There is one important point which Major Sugar has apparently not touched on, namely, the postoperative interval after which his final determinations on the degree of correction afforded were made. In my own experience, changes have occurred up to six months after operation, and any determination of correction prior to that time should accordingly be considered tentative.

LIEUTENANT COLONEL EDWIN N. BEERY,
Medical Corps, Army of the United States.

96 Remsen Street, Brooklyn.

Obituaries

CHARLES H. MAY, M.D.
1861-1943

In the passing of Dr. Charles H. May, ophthalmology has lost an outstanding figure, a great teacher and a physician of unsurpassed integrity. His death on Dec. 7, 1943, in the eighty-third year of his life, occurred exactly one month after the celebration of his golden wedding anniversary. His life was a long and full one, replete with the satisfactions that came with years of service to his fellow men.

Charles Henry May, the son of Henry May and Henrietta Oppenheimer May, was born in Baltimore on Aug. 7, 1861. Four years later his family moved to New York city, his future home. A brilliant student, young Charles led his class in the private and public schools he attended, as well as at the College of the City of New York. Too young to enter medical school and the career of medicine on which he had set his heart, he entered the College of Pharmacy of the City of New York, graduating at the head of his class in 1879, with the award of a gold medal. He enrolled in Columbia University College of Physicians and Surgeons, graduating with the degree of Doctor of Medicine in June 1883, with the first Harsen Prize for Clinical Reports and the first Harsen Prize for Proficiency at Examination. The title of his graduation thesis was "Statistics of Four Hundred Cases of Rheumatism Treated at the Roosevelt Hospital," a subject suggested by Dr. William H. Draper. Dr. May's brilliant scholastic record led to his nomination, without further examination, to the position of junior assistant to Bellevue Hospital, with the choice of the medical or the surgical side, according to a formal letter from Dr. John G. Curtis, secretary of the faculty of the College of Physicians and Surgeons. The young physician declined this offer, since he had received and accepted an appointment at Mount Sinai Hospital to the medical division, under Dr. E. G. Janeway, Dr. Alfred Meyer and Dr. Rudisch Heinemann.

After leaving Mount Sinai Hospital, he went into private practice, in 1885, with an office on East Fifty-Eighth Street. He worked with Sequin in nervous diseases, Delafield in internal medicine and Agnew in ophthalmology. Dr. May's decision to enter the specialty of diseases of the eye was influenced by the kindness and friendship of Cornelius R. Agnew, professor of ophthalmology at Columbia University College of Physicians and Surgeons.

By 1887 Dr. May had accumulated enough money to go to Europe. He spent six months at Halle, Germany, studying the eye and ear under Alfred Graefe and Hermann Schwartze, and then spent a month visiting the ophthalmic clinics of Berlin. During this period, he met Hermann von Helmholtz and received permission to translate his book on "Physiological Optics." This project failed because no American publisher would undertake to bring out the book.

Six months were spent in the Vienna clinics of E. Fuchs, Dimmer, Koenigstein, Politzer and Urbantschitch. On his way home, Dr. May spent a few weeks in Paris, visiting the clinics of Landolt, Galezowsky, de Wecker and Panas, and in London, at Moorfields.

Returning to the United States in 1888, he opened an office in New York city, on Madison Avenue at Fifty-Ninth Street, later moving to the house he purchased at 698 Madison Avenue. First he practiced both otology and ophthalmology, receiving appointments at the Manhattan Eye and Ear Infirmary, the New York Ophthalmic and Aural Institute and the College of Physicians and Surgeons. Soon after Agnew's death in 1888, Dr. May resigned from the first-named appointment and spent his hours in the clinics at the last two institutions, destined to become the Herman Knapp Memorial Hospital and the Vanderbilt Clinic. He became chief of clinic at the Vanderbilt Clinic after the resignation of Dr. John E. Weeks, holding that position until 1903. Dr. May became associated with the New York Polyclinic Hospital, lecturing in ophthalmoscopy and diseases of the eye from 1886 to 1890. At Mount Sinai Hospital, he was made an assisting attending physician in the department of ophthalmology in 1893, becoming a full attending physician later, when Dr. Gruening retired.

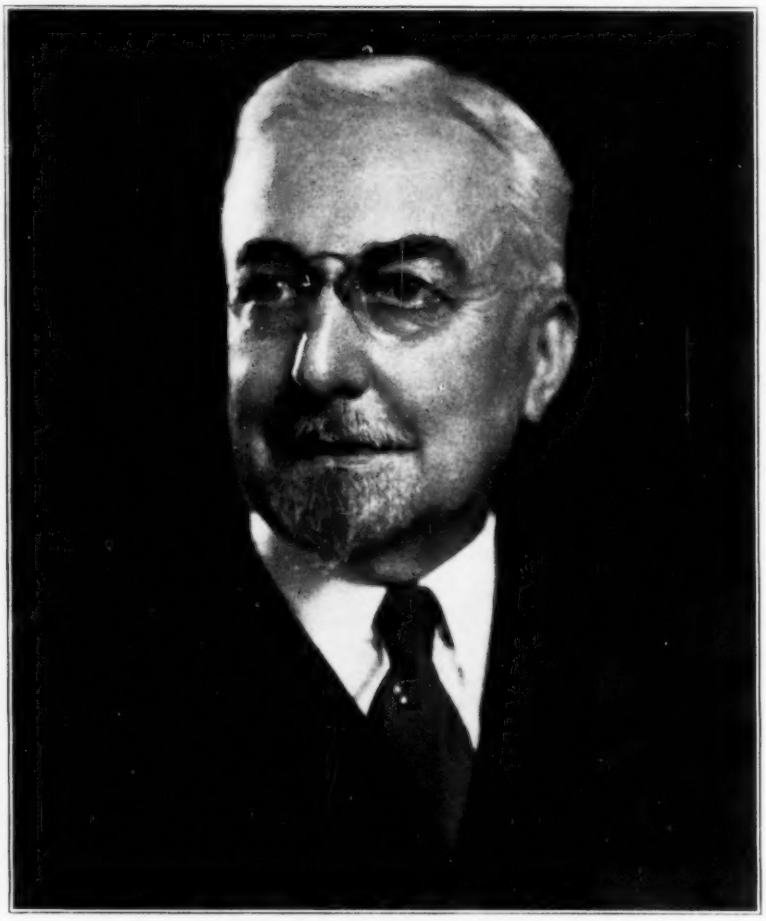
In 1914 he was asked to establish an ophthalmologic service at Bellevue Hospital, where a ward of forty-five beds was equipped according to his plans. He remained as director of this service until 1925, when he resigned, to be succeeded by Dr. John M. Wheeler. Thereafter he was consulting ophthalmologist to Bellevue,

Mount Sinai, French and Monmouth Memorial Hospitals.

His private practice was large, and in his later years he was assisted in his work by young associates, among them Dr. William B. Doherty, Dr. Edward Bassen and, since 1935, a nephew, Dr. Charles A. Perera. Medical visitors from all over the world visited his office, many from among those whom he had taught to use the ophthalmoscope and to recognize diseases of the eyes.

Dr. May often stated that the man who knew more about ophthalmology than any one with whom he was ever associated was Herman Knapp. Dr. May's obituary of Knapp, published in *Ophthalmology* **7:** *727* [July] 1911, revealed the admiration of a devoted friend and follower for a great teacher.

In 1900 Dr. May devised an improved double disk ophthalmoscope (*Ann. Ophth.* **9:** 73 [Jan.] 1900), and in 1914 he reported on a new electric ophthalmoscope (*New York M. J.* **100:** 229 [Aug. 1] 1914), with replacement of the customary fragile mirror by a solid piece of glass, which acts both as a condenser and as a reflector, and the addition of a convex condensing lens immediately above the lamp. This improvement in the electric ophthalmoscope, which William S. Dennett had invented in 1885, was given to the medical profession by its inventor and is now in general use.



CHARLES H. MAY, M.D.
1861-1943

In 1893 he married Rosalie Allen, who, together with his two sisters, Mrs. Florence Oppenheimer and Mrs. Nellie Mosbacher, survives him.

He was a member of the American Ophthalmological Society, the American Academy of Ophthalmology and Otolaryngology, the New York Academy of Medicine, the American College of Surgeons, the American Medical Association and the New York State and County Medical Societies.

In the field of medical writing Dr. May was a master. His most widely known work is his

"Manual of the Diseases of the Eye," which has gone through eighteen editions since 1900, the last three revisions having been produced with the assistance of Dr. Charles A. Perera. This book is in wide use as a textbook for medical students and general practitioners of medicine, and it has been translated into many foreign languages, the most recent one being the Portuguese. To Dr. May his textbook was a real child. He read the ophthalmologic literature assiduously, ever seeking to keep his book up-to-date. Just two weeks before his death, he insisted on completing the correction of proof of the eighteenth edition of his brain child.

It is not generally known that Dr. May's first book was "Diseases of Women," published in 1885 by Lea Bros. & Co., Philadelphia. This book was well received and went into a second edition, revised by Leonard S. Rau in 1890. During his early years of practice, Dr. May compiled several textbooks for grammar schools on anatomy, physiology and hygiene, published by William Wood & Co., New York, which went through several editions, the last in 1896. He also wrote, with Dr. Charles F. Mason, an index of materia medica in 1887. He wrote on ophthalmic subjects for the "International Encyclopedia," the "Reference Handbook of the Medical Sciences" and for a number of lay periodicals.

Dr. May was an artist of ability in painting lesions of the fundus and illustrated not only his own writings but those of several colleagues.

He was a skilful surgeon and able therapeutist in his chosen field. He was one of the first in this country to report, in 1899, on the restoration of the conjunctival cul-de-sac in a case of total symblepharon by means of Thiersch skin grafts, and, in 1901, the restoration of a socket by the use of a large Wolff graft. He published papers on the prevention and treatment of ophthalmia neonatorum in 1895, 1906 and 1908.

Physically active until he sustained a fracture of the leg, in an automobile accident in 1910, which delayed in uniting, he was compelled to give up the walks which were one of his relaxations. His main extraprofessional hobbies were limited to visits with his friends, the enjoyment of good cigars, an occasional game of bridge, the reading of detective stories and summer travels in Europe. He crossed the Atlantic every summer for many years, making in all fifty-four trips. He often visited the home of his friend, E. Fuchs, who returned the visits on his trips to this country.

During the World War of 1914-1918 his crippled leg prevented his serving his country in the armed forces. His colleagues in service received from Dr. May, when they returned to their practices, checks for the full fees he had collected from their patients.

As a consultant, he was superb, both in the handling of patients and in arriving at careful diagnoses and decisions. His opinions were of great value because they were based on a complete study of the problem, conservative judgment and vast experience. He was always careful to preserve the reputation of his colleagues and made every effort to have patients return to their former oculists when they came to him for his advice. His ethical standards were so high and his deeds so closely approximated his ideals that he was an inspiring model to watch and follow.

His ability and impartiality were so well recognized that he was employed by governmental agencies, industrial groups, insurance companies and injured workmen to investigate ocular injuries and give an honest verdict. As a special witness in court, he always commanded respect because of his knowledge, experience and integrity. He had a profound disgust for the few colleagues he encountered who perjured themselves in court and took sides without regard to truth and justice.

In handling patients he was without a peer. He knew when to reassure, when to be sympathetic and when to be firm. Patients with a hopeless prognosis were given a feeling of courage by his words.

Like all great men, his kind and generous deeds were hidden. No one who sought his help was turned away.

CHARLES A. PERERA.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Anatomy and Embryology

ANATOMIC FACTORS THAT INFLUENCE THE DEPTH OF THE ANTERIOR CHAMBER: THEIR SIGNIFICANCE. H. S. SUGAR, Am. J. Ophth. **25:** 1341 (Nov.) 1942.

Sugar draws the following conclusions:

"1. As age advances, the crystalline lens increases in size, thus decreasing the axial depth of the anterior chamber.

"2. The depth of the anterior chamber appears to have a definite relationship to the refractive error of the eye. Myopic eyes tend to have deeper anterior chambers whereas the hyperopic have relatively shallower chambers. This is related to the axial length of the eyeball.

"3. The importance of the anatomic factors in the etiology of acute glaucoma is emphasized. They are significant in making possible measures for the prevention and early detection of this condition."

W. S. REESE.

Congenital Anomalies

UNILATERAL MELANOSIS IRIDES. R. E. R. MITTON, Indian J. Ophth. **4:** 5 (Jan.) 1943.

A Punjabi woman aged 34 had a light golden brown iris in the right eye, while the iris of the left eye was partly golden brown and partly African brown. Biomicroscopic examination showed that the texture of the iris in the melanotic areas differed from that in the lighter areas in that it presented small mamillations. These elevations were close together and entirely confined to the deeply pigmented areas. They seemed superficial, but the deeper stroma was also heavily pigmented.

The pupils dilated unequally, and the pupil of the left eye had a straight upper border; that is, the part of the iris which was pigmented throughout its width underwent less contraction than the part in which the melanin was less evenly distributed. Refraction showed mixed astigmatism.

W. ZENTMAYER.

Cornea and Sclera

NODULAR KERATITIS. O. H. ELLIS, Am. J. Ophth. **25:** 1224 (Oct.) 1942.

Ellis reports a case of nodular keratitis observed from its incipiency. The patient's mother, 2 aunts, 2 sisters, a niece and probably her paternal great-grandfather all suffered from the condition. Surgical treatment did not improve the vision. Since the condition began with the onset of the menses and the pain ceased during two pregnancies, Ellis feels that it may have been due to an endocrine imbalance.

W. S. REESE.

WHITE RINGS IN THE CORNEA (COATS). J. WALDMAN, Am. J. Ophth. **25:** 1362 (Nov.) 1942.

Waldman concludes that white rings in the cornea (Coats) occur more frequently than the literature indicates, and suggests routine biomicroscopic examination as a means by which their incidence and causation may be learned.

W. S. REESE.

A Case of Fistula of the Cornea: A Method of Treatment. J. B. McArevey, Brit. J. Ophth. **27:** 306 (July) 1943.

McArevey records a case of traumatic fistula of the cornea in a man aged 27. Fluorescein aided in confirmation of the diagnosis. The diameter of the hole was uniform and measured 1 mm. On the basis of the assumption that with so slight a loss of tissue the swelling of the corneal stroma might close the hole and allow cicatrization to take place if the sides of the fistula were freshened up, a series of perforations were made into the clear portion of the cornea just outside the opacity with a discission needle; these perforations were intended to enter the fistula at different levels. In addition, three small incisions were made into the corneal stroma with a Ziegler knife. A fine probe was passed into these openings, and the corneal tissue was pushed toward the fistula. The anterior chamber had reformed in forty-eight hours.

W. Zentmayer.

Glaucoma

Aqueous Veins. K. W. Ascher, Am. J. Ophth. **25:** 1301 (Nov.) 1942.

Ascher finds that appearance of the glass rod phenomenon in aqueous veins is extremely rare in eyes with primary compensated glaucoma as compared with its induction in normal eyes. He discusses the effect of drugs on aqueous veins and stresses the importance of these veins in the understanding of the problems of glaucoma.

W. S. Reese.

Injuries

Changes in the Ciliary Body After Contusio Bulbi in Which Only the Anterior Segment of the Eye Is Affected. G. L. Kilgore, Am. J. Ophth. **25:** 1095 (Sept.) 1942.

Kilgore gives the following summary:

"1. Sections of eyes that have suffered experimental contusio bulbi have been presented to show the pathology found in the ciliary body after contusions.

"2. Symptoms following even minor blows to the front of the eye can be explained by the cyclitic changes.

"3. Atrophy of the ciliary body may explain some of the prolonged visual disturbances.

"4. The prognosis should be guarded in cases of contusion. Insignificant blows may be followed by a permanent visual disability.

"5. A case report is submitted to illustrate the practical correlation of pathologic and clinical observations."

W. S. Reese.

"Arc Flash" Conjunctivitis, Actinic Conjunctivitis from Electric Welding Arc. F. E. Rieke, J. A. M. A. **122:** 734 (July 10) 1943.

Rieke considers it unfortunate that the term "arc flash" has been given to ultraviolet conjunctivitis, as it implies that the conjunctivitis is commonly incurred through the incaution or unguarded exposure of the eyes to the flash of the welder's first brilliant contact spark and thus is an instantaneous affair. This can occur, but the injured person must be very close to the arc, within 1 or 2 feet (0.3 or 0.6 meter), and this infrequently happens. It is so usual as to be the rule that the painful eyes of "arc flash" result from an excessive exposure to the arc over a minimum of several minutes, more commonly several hours of time spread through the working shift. It is a cumulative injury, similar in pathogenesis to that of snow blindness and sunburn, which obviously are quantitatively related to the pigmentation of the skin and the length of time spent in the sun's rays.

The author gives the following summary: "Actinic conjunctivitis, or 'arc flash,' as seen in the Oregon Shipbuilding Corporation and the Kaiser Company, Inc., Portland, among 57,000 shipyard workers exposed at various times to the emanations from electric arc welding, is defined as a conjunctivitis caused by excessive exposure to the welder's electric arc and characterized by delayed onset, self-limited course of twenty-four hours, pronounced bulbar hyperemia, swelling of the lids, slight 'sunburn' of the face, absence of discharge other than tears, extreme photophobia and a feeling of sand in the eyes.

"Treatment is given for relief of symptoms through dark glasses, cold applications and the use of local anesthetic, vasoconstricting, mydriatic, lubricating and sedative preparations.

"Prophylactic measures are outlined for the patient and his environment which can completely prevent occurrence of the injury." W. ZENTMAYER.

TREATMENT OF PHOTOPHTHALMIA FOLLOWING EXPOSURE TO RAYS OF WELDING ARC. C. E. BENSON, U. S. Nav. M. Bull. **41:737** (May) 1943.

Benson directs attention to the problem of exposure of the eyes to the radiant energy of the welding arc with the resultant photophthalmia. This type of injury to the eyes, also called actinic ray ophthalmia or "flash," is frequent in shipyards and in plants where welding plays a large part. It is not the welder who is the most frequent victim of his own arc but the workman engaged in work near the welder. The welder protects himself with his hood. He may, however, receive an injury from the actinic rays of the arc of another welder near him or from his own "accidentally struck" arc while his own hood is raised. After exposure to the arc a latent period follows, which may vary from two to fifteen hours. The lesion then manifests itself with sudden onset of intense photophobia, lacrimation and a burning sensation in the eyes. The most frequent complaint is that of a feeling of "sand in the eyes." The lesion is bilateral, although at times the symptoms appear earlier in one eye than in the other; in the present series the majority of "one-eyed flashes" were caused by foreign bodies. The conjunctival vessels are moderately dilated, but this congestion is usually limited to the area of the palpebral fissure. Prevention can be accomplished by protection of the eyes with a shield, hood or goggles. Seventy-three patients were treated with 2 per cent butacaine sulfate and 1 per cent diothane hydrochloride, and 447 patients, with a solution containing 0.25 per cent nupercaine hydrochloride and 0.5 per cent neo-synephrine hydrochloride as the active principles. The nupercaine was used because of its relatively prolonged anesthetic action. Neo-synephrine was added to overcome the vasodilatation and to neutralize partially the contraction of the pupils accompanying many lesions produced by actinic rays. The nupercaine–neo-synephrine solution was dissolved in an aqueous base of zephiran chloride (1:5,000) to decrease the surface tension of the solution, to produce better penetration and to furnish an antiseptic medium. About 2,500 additional patients were treated by the nupercaine–neo-synephrine routine. The treatment did not appreciably decrease the duration of the reparative process. It gave considerable symptomatic relief and helped in the return of men to their work with a minimum of lost time and with no apparent permanent injury.

J. A. M. A. (W. ZENTMAYER).

TRAUMATIC OEDEMA OF THE MACULA. S. PHILPS, Brit. J. Ophth. **27:305** (July) 1943.

Philps reports 4 cases of commotio retinae because they represent four stages in the progress of macular edema—edema of the macula, edema replaced by pigmentary changes, hole formation and retinal detachment.

W. ZENTMAYER.

Instruments

A Modification of Arruga's Speculum. H. Neame, Brit. J. Ophth. **27:** 310 (July) 1943.

For operation in cases of detachment of the retina, Arruga's speculum of plated metal was taken as a model, and an instrument made of plastic material was designed 2 mm. wider than the original, so as to give a larger field within the hollow of the retractor for the application of diathermy in treatment of the condition.

The plastic material is roughened for a small area on its convex surface and for a larger area in the hollow of the concave side. Light enters from a small battery or through a transformer from the main at the handle, is carried by internal reflection to the end of the instrument and is dispersed only when it meets the roughened surface. The retractor, of course, is quite free from heat. The illumination of the area of the sclera requiring treatment is admirable and entirely obviates the presence of any shadows. The greater width of the speculum is also an advantage. The third, and definite, advantage of this instrument is that it is a nonconductor of electricity. The article is illustrated.

W. Zentmayer.

Operations

A New and Improved Technique for the Closure of Cataract Incisions. C. H. DeVaul, Am. J. Ophth. **25:** 1079 (Sept.) 1942.

DeVaul describes a rather involved method for suture of cataract incisions. He first circumsizes the upper two fifths (his illustration appears to show at least three fifths) of the cornea and undermines the conjunctival flap. He then fashions two scleral flaps at the upper limbus and inserts sutures so that the conjunctiva as well as the sclera is closed when these sutures are tied after the extraction. These sutures are then laid aside, and the incision is made as usual, the knife being brought out between the scleral flaps. After extraction of the lens the sutures are drawn tight but not tied until reposition of the iris pillars is effected.

W. S. Reese.

Physiology

Gonioscopic Study on the Canal of Schlemm. P. C. Kronfeld, H. I. McGarry and H. E. Smith, Am. J. Ophth. **25:** 1163 (Oct.) 1942.

The authors draw the following conclusions from their studies on Schlemm's canal.

"1. Following a sudden lowering of the intraocular pressure induced by aspiration of aqueous or compression of the globe by means of an ophthalmodynamometer, the canal of Schlemm becomes gonioscopically visible in nonglaucomatous eyes, blood taking the place of the usual colorless contents.

"2. Pressure exerted upon the eyeball by the contact lens is not conducive to eliciting this phenomenon but rather to effacing it.

"3. Eyes affected with wide-angle glaucoma show the filling of Schlemm's canal, either in an atypical form or after greater drops in intraocular pressure than are required to induce the phenomenon in nonglaucomatous eyes, or they fail to show it altogether."

W. S. Reese.

Some Observations and Experimental Studies on the Physiology of the Ciliary Muscle. E. Sachs, Am. J. Ophth. **25:** 1277 (Nov.) 1942.

Sachs gives the following summary:

"1. A backward movement of the anterior coronal region of the ciliary body was demonstrated to be a normal component of the ciliary-muscle contraction in both

dogs and cats. A narrow neutral zone separated this backward-moving region from the forward-moving tissue of the posterior part of the ciliary body and that of the choroid.

"2. The distance of the neutral zone from the limbus varied from 2.0 to 5.0 mm. in 11 dogs, and from 4.0 to 7.0 mm. in 6 cats.

"3. The extent and distribution of the backward and the forward movement (in 11 and 33 eyes, respectively) were measured along a meridian. Some eyes showed a definite peak, while others exhibited a homogeneous distribution of movement.

"4. The contraction time in the dog was about 5 seconds as compared with 3 seconds in the cat (seven and five eyes, respectively).

"5. The force of contraction producing the main (forward) movement in a narrow (about 1.75-mm.) strip of uvea was balanced by a second force, of known magnitude in milligrams. A pull of more than 200 mg. (the maximum recordable by the instrument) was not infrequently found.

"6. No significant difference in force was found between the temporal and nasal sectors.

"7. The elastic resistance offered by a strip of choroid about 1.75 mm. wide to a minimally distortive longitudinal pull was measured in nine eyes and found to be 14.0 to 33.0 mg. in the dog and 14.0 to 24.0 mg. in the cat. Measurements of the resistance in the posterior part of the choroid during stimulation of the ciliary muscle showed no change.

"8. The influence of the intraocular pressure on the contraction of the ciliary muscle was studied in six cat eyes. There was a definite impairment of muscle efficiency at 80 mm. Hg, while no influence could be demonstrated between 11 mm. and 60 mm. Hg.

"9. The significance of these findings is discussed." W. S. REESE.

Refraction and Accommodation

MYOPIA. A. COWAN, Am. J. Ophth. **25:** 844 (July) 1942.

Cowan disagrees with Donders' statement that because an eye is myopic it must be considered unsound. He cites the conflicting theories of the cause of myopia and its distribution. He insists that myopia is a simple error of refraction and that the terms "pathologic," "malignant" and "pernicious" should be abandoned, as they indicate some disease that either occurs with or happens to result in myopia. He believes in the full correction of myopia and emphasizes the importance of prevention of disease in myopic eyes. W. S. REESE.

Retina and Optic Nerve

ANGIOID STREAKING OF THE RETINA. L. LEHRFELD and S. S. BRAV, Am. J. Ophth. **25:** 1222 (Oct.) 1942.

Lehrfeld and Brav report 2 cases of angioid streaks of the retina associated with pseudoxanthoma elasticum in sisters. W. S. REESE.

CHORIORETINITIS ASSOCIATED WITH POSITIVE SEROLOGIC TESTS FOR TOXOPLASMA IN OLDER CHILDREN AND ADULTS. D. VAIL, J. C. STRONG and W. V. STEPHENSON, Am. J. Ophth. **26:** 133 (Feb.) 1943.

The authors give the following summary:

"Six cases of chorioretinitis of previously unknown etiology are reported in which the presence of positive neutralization antibodies for Toxoplasma was proved. The condition may be either congenital or acquired. The only symptom may be that

of poor or decreasing vision. The fundus usually reveals a chorioretinitic lesion, unilateral or bilateral, having a predilection for the macular area. It has a grayish-white center, is irregular, bordered with dark pigment, and surrounded on one or more sides by faint choroidal hemorrhage. The spread of the lesion is usually in the direction of the hemorrhage. The lesion may be elevated. Iridocyclitis, vitreous opacities, retinitis proliferans, and detachment of the retina may result. Central vision is always adversely affected."

W. S. REESE.

THE DETECTION AND SIGNIFICANCE OF MELANOPHORE EXPANDING SUBSTANCE IN URINE AND BLOOD WITH SPECIAL REFERENCE TO RETINITIS PIGMENTOSA. J. R. MUTCH and D. MACKAY, Brit. J. Ophth. **27:** 434 (Oct.) 1943.

Mutch and Mackay give the following summary:

"The literature on the possible rôle of B-hormone in vision and its relationship to the pathogenesis of retinitis pigmentosa is briefly reviewed, and the techniques for the assay of B-hormone are discussed.

"The results of several urinanalyses for B-hormone are summarised. Reasons are quoted for considering the present assays for B-hormone as not completely specific.

"Experiments are reported in which blood samples from 9 retinitis pigmentosa patients were assayed and compared with blood samples from 7 normal controls. Details are given of the process of extraction and assay employed. Only 3 of the 9 retinitis pigmentosa samples were definitely 'positive.' Two of the 7 control samples gave a positive result.

"It is concluded that the blood of retinitis pigmentosa patients does not regularly contain a melanophore-expanding substance and that such a substance may occasionally be present in 'normal' bloods.

"A further experiment is described showing that in the rabbit B-hormone injected intravenously disappears very rapidly from the circulation."

W. ZENTMAYER.

SUB-HYALOID HAEMORRHAGE FOLLOWING "T. A. B." INOCULATION. J. P. F. LLOYD, Brit. J. Ophth. **27:** 461 (Oct.) 1943.

A man aged 36, of normal physique and previous good health, received an injection of a bacterial vaccine containing 500,000,000 typhoid and paratyphoid A and B bacilli and fifteen days later a second injection containing 1,000,000,000 bacilli. Each dose produced a normal reaction. The day after the second injection he noticed that vision in the left eye was extremely poor. When he was examined two weeks later vision in this eye was limited to hand movements. An extensive subhyaloid hemorrhage lay in front of the macular region. Three months later there was considerable unabsorbed hemorrhage in the vitreous. The right eye remained normal throughout. Physical examination showed chronic bronchitis. The blood picture was normal.

W. ZENTMAYER.

DIABETIC RETINITIS. J. H. DOGGART, Brit. M. J. **2:** 212 (Aug. 14) 1943.

In a letter concerned with the diet in diabetes (*Brit. M. J.* **2:** 115 [July 24] 1943), Dr. George Graham stated: "The complication I dread in diabetes is that of retinitis and cataract. Hyperglycaemia is not the only factor in the production of these conditions, and I have seen retinitis develop in elderly diabetics although the blood sugar has been well controlled. I have much more often seen it in patients who have had an uncontrolled diabetes for some years, and I have watched the retinitis improve when the diabetic condition has been brought under control. I believe that patients who are allowed to have a blood sugar above 250 or 300 mg. throughout the day run much greater risks of this complication."

This led Doggart, in reply, to question the possibility of improvement in diabetic retinitis with treatment. In none of the cases of defective vision due to diabetic retinitis which he has seen has any appreciable restoration been shown, however soon the diabetic condition was brought under control by diet or other measures. He put the question to a number of his ophthalmologic colleagues, and none of them remembered having seen improvement in defective vision attributable to diabetic retinitis. Doggart suggests that appreciable improvement in diabetic retinitis must be extremely rare as compared with the deterioration of vision, which progresses steadily in spite of all known means of adjusting the victim's disordered metabolism.

ARNOLD KNAPP.

DIABETIC RETINITIS. R. D. LAWRENCE and WILFRID OAKLEY, Brit. M. J. **2**: 312 (Sept. 4) 1943.

The authors, who are associated with the diabetes clinic, King's College Hospital, think that the difference in the experience of Mr. J. H. Doggart and Dr. George Graham (*Brit. M. J.* **2**: 212 [Aug. 14] 1943) can be explained by the fact that the latter are referring to different phases of the same disease. When the usual case comes to the attention of the ophthalmologist because of defective vision, the disease is well advanced and extensive exudates are present, which can rarely be influenced by treatment. On the other hand, in the routine ophthalmic examination of diabetic patients much earlier stages of retinitis are frequently seen, with hemorrhages and small exudates, and these patients are often kept under observation for five or more years without appreciable change in vision being evident; in fact, the earliest stage, that of small hemorrhages, may completely disappear under vigorous treatment with insulin.

Of 1,500 diabetic patients with retinal lesions, 50 have lost all hemorrhages or show an occasional small one from year to year, without injury to vision. In the vast majority, many of them with large exudates, the condition of the eyes has become slowly and progressively worse, total blindness, however, being rare; in an unfortunate small minority, often among the fairly young with well controlled diabetes, retinitis proliferans has mysteriously developed, with rapid loss of vision. The rare cases of retinitis in adolescents have usually been among those whose disease was uncontrolled, the retinal lesions having developed during the worst phase, and the retinal complication was then checked by better control of the diabetes. The authors conclude that careful treatment of diabetes is most important; it may even remove the retinal condition, but more often only checks its progress.

ARNOLD KNAPP.

Tumors

EPITHELIAL TUMORS OF THE LIMBUS. J. E. ASH and H. C. WILDER, Am. J. Ophth. **25**: 926 (Aug.) 1942.

From a study of 93 pure epithelial tumors arising at or near the limbus, Ash and Wilder draw the following conclusions:

"1. Epithelial 'tumors' of the limbus in adults are frequently simply leukoplakic metaplasia of conjunctival epithelium.

"2. Papilloma or squamous-cell carcinoma may develop secondarily in this altered epithelium.

"3. Basal-cell carcinoma is rare at the limbus.

"4. The tendency is to involvement of the corneal epithelium rather than to extension peripherally.

"5. Penetration of the sclera and metastasis are rare even in large carcinomas.

"6. The pathologic diagnosis of 'carcinoma' is not necessarily an indication for irradiation in connection with radical surgery. Enucleation of the eye appears

to be justified only where there is already appreciable involvement of the cornea, or after local excision has failed.

"If one must have a cancer, the limbus would seem to be as safe a place as any to have it."

W. S. REESE.

ORBITAL METASTASIS FROM TUMOR OF THE PANCREAS. H. R. SNIDERMAN, Am. J. Ophth. **25:** 1215 (Oct.) 1942.

Sniderman briefly reviews the literature of carcinoma of the orbit and reports 2 cases of primary carcinoma of the pancreas with orbital metastases. In both cases the left orbit was involved and the first symptoms were diplopia. Reports of necropsy are given.

W. S. REESE.

KRÖNLEIN OPERATION FOR A CASE OF CYST OF THE OPTIC NERVE. J. HANSRAJ, Indian J. Ophth. **4:** 6 (Jan.) 1943.

A middle-aged woman had noticed gradually increasing protrusion of the right eye, with loss of vision. There was pronounced exophthalmos, with bulging of the conjunctiva in the lower cul-de-sac and restricted movements of the globe. Vision consisted in ability to count fingers at 5 feet (152 cm.). There was papilledema. A roentgenogram showed that the right orbit was larger than the left. A Krönlein operation was performed, and when Tenon's capsule was incised fluid escaped. Further dissection revealed a cyst the walls of which were firmly adherent behind the inner surface of Tenon's capsule. Later the exophthalmos returned. A long bent needle was passed into the retrobulbar region, and 3 cc. of fluid was withdrawn. The condition recurred and was treated in the same manner, with apparent cure. Visual acuity was 6/6.

W. ZENTMAYER.

Vision

VISUAL PROBLEMS: CERTAIN ASSUMPTIONS AND DATA. W. T. HUNT and E. A. BETTS, Am. J. Ophth. **25:** 1084 (Sept.) 1942.

After a study of 126 fifth grade pupils, Hunt and Betts summarize their results and make the following conclusions:

"The findings of this study indicate clearly the need for additional studies on the seeing problems of individuals at various age levels. These problems should be defined by means of comprehensive visual-analysis techniques. Studies reported heretofore have been cursory in nature.

"If the findings reported herein are verified by subsequent studies, then serious thought should be given to preventive measures. It may become necessary to appraise the near-point seeing tasks imposed upon elementary school children. Sustained reading activities may produce visual inefficiency, especially among school children.

"Evidences of toxic conditions uncovered in this study lead to the conclusion that the relationship between health factors and efficient seeing should be studied. In the larger sense, seeing is a psycho-physiologic process. Strictly anatomic concepts of seeing appear to circumscribe thinking and practice."

W. S. REESE.

NIGHT BLINDNESS, IMPROVEMENT WITH VITAMIN D: INCLUDING EXPERIMENTAL PRODUCTION OF RETINITIS PIGMENTOSA AND ITS TREATMENT IN HUMANS WITH VITAMIN D. A. A. KNAPP, U. S. Nav. M. Bull. **41:** 373 (March) 1943.

Knapp states that of all ocular conditions giving rise to night blindness, retinitis pigmentosa stands at the forefront. Fortunately, it is a rare disease. Night blindness may be caused by a deficiency of at least two vitamins, A and D. Another condition often complicated by night blindness is myopia. Of 93 patients with various

degrees of myopia, 64 complained of poor vision under conditions of reduced illumination. As routine treatment these 64 patients were given 60 drops (13,860 U. S. P. units of vitamin D) of synthetic oleovitamin D U. S. P. and at least 1 Gm. of available calcium. With some the dose of synthetic oleovitamin D was increased to 200 drops daily. After six to twenty-seven months of observation, during which time the patients were examined at least once a month, 20 patients showed actual reduction of the myopia. Casts of the anterior segment of many of the eyes, and in 1 instance a photograph of the fundus before and after treatment, proved beyond doubt that both the anterior and the posterior segment of the eyeball may shrink after treatment with vitamin D and calcium. Of the 64 persons suffering from poor vision at night, 48 noticed distinct improvement with respect to their nyctalopia which was in no way dependent on their myopic status. Several weeks usually elapsed before clinical improvement was definite. The majority of the patients whose myopia was reduced spoke of their greater ability to see after nightfall, and others had better vision at night when their myopia was stationary, or even in the presence of an increase in their near sightedness. The condition of 16 patients apparently remained the same. During the treatment of both the patients with retinitis pigmentosa and those with myopia toxicity was watched for. Seldom did a toxic sign develop—a mild rash, nausea, vomiting or constipation might appear—but these symptoms disappeared soon after the medication was discontinued or reduced.

J. A. M. A. (W. ZENTMAYER)

A STANDARDIZED COLOR-VISION TESTING LANTERN (II), TRANSPORT TYPE. L. C. MARTIN, Brit. J. Ophth. **27:** 255 (June) 1943.

A modification of the standardized color vision–testing lantern designed by Martin in 1939 has been made to render it suitable for use in transport undertakings. Experience has shown, however, that the mariner's test was a satisfactory one. The modification consists of an orange-yellow filter in addition to the original red, green and white of the first form, so that pairs of red and orange and orange and green lights can be shown. Trials with the smallest apertures and standard conditions then showed that normal persons with good color vision sometimes made mistakes—for example, a combination of green and orange might be called "green-red" or one of orange and red be called "white-red." It is necessary, therefore, when the smallest apertures (0.02 inch [0.05 cm.]) are used to restrict the lights shown to red, green and white, as in the well established mariner's test; this is even more important when the modifying glasses are used with the small apertures.

When the apertures were enlarged to a diameter of 0.05 inch (0.13 cm.), the distinctions were easy with normal vision, and this suggested the use of a diameter of 0.04 inch (0.1 cm.) as a standard for the pairs of apertures with which the supplementary part of the test are conducted.

W. ZENTMAYER.

Therapeutics

GENERAL AND LOCAL ADMINISTRATION OF PENICILLIN. M. E. FLOREY and H. W. FLOREY, Lancet **1:** 387 (March 27) 1943.

The first part of this paper deals with various methods of administration of penicillin in cases of osteomyelitis, septicemia, empyema and subacute bacterial endocarditis. Intramuscular injection was found to be a safe, and the most practical, method of administration.

The local application of penicillin, which is discussed in the second part of the paper, is concerned chiefly with external infections of the eye. Treatment consisted of repeated application of ointments, and occasionally of aqueous solutions, containing calcium penicillin in a strength of 600 to 800 units per gram. In the 46 cases of blepharitis, chiefly infections with Staphylococcus aureus, the response

was good, but apparently no previous treatment had been attempted. In 7 cases recurrence of the infection cleared up with continued treatment. In 18 cases of acute conjunctivitis, in 6 of which the infection was complicated by corneal ulcer, Staphylococcus albus, Staph. aureus and Bacillus coli were listed as causative organisms. Of 5 cases of ophthalmia neonatorum, Staph. aureus was found in 2 and the gonococcus, B. coli and an unknown organism in 1 each of the remaining cases. The corneal ulcers healed in five to seven days except in 2 cases, in 1 of which there occurred a hypopyon of unknown origin and in the other a ring ulcer due to B. coli. The conjunctivitis disappeared in one to five weeks, and the ophthalmia, within one week.

In the 19 cases of chronic conjunctivitis the condition had not responded to previous treatment, lasting one month to several years; in all but 1 of these cases recovery was obtained with penicillin in one to nine weeks. In 6 cases of dacrocystitis a solution of penicillin was injected five times a week. Cultures taken on the eighth day were sterile, and clinical recovery occurred in 3 cases.

The authors emphasize the necessity of repeated applications of penicillin at short intervals in order to obtain a rather constant bacteriostatic concentration of the drug. It is advisable to continue the treatment for some time after an apparent clinical cure.

L. VON SALLMANN.

Society Transactions

EDITED BY DR. W. L. BENEDICT

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

FRANK C. KEIL, M.D., *Chairman*

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Nov. 15, 1943

Spielmeyer-Vogt Disease: A Study of Its Pathology. DR. ISADORE GIVNER AND DR. LEON ROIZIN (by invitation).

Monocular Exophthalmos Due to Hyperthyroidism in a Patient with the Duane Syndrome. DR. W. GUERNSEY FREY.

A white woman aged 48 presented the Duane syndrome in the left eye. There were absence of abduction, narrowing of the palpebral fissure and retraction of the globe on her looking to the right. The movements of the right eye were normal.

A toxic goiter developed three years ago, followed a year later by exophthalmos, which was more prominent in the right eye. Thyroidectomy relieved all the symptoms of hyperthyroidism except the exophthalmos, which measured 28 mm. in the right eye and 25 mm. in the left eye. The sclera was not exposed above or below the cornea in either eye. The lids were incompletely closed during sleep, but the cornea was not exposed. The lids of the left eye showed brawny edema or fatty swelling. Vision remained 20/25 in both eyes without correction.

With the development of exophthalmos, the fibrous condition of the external rectus muscle of the left eye probably interfered with the circulation of the lids, with resultant edema and swelling. It also prevented the exophthalmos from being as prominent as that of the other eye.

The case is reported as one representing a hitherto unrecorded cause of monocular exophthalmos.

Changes in the Fundus of the Eye Associated with Various Forms of Arterial Hypertension. DR. HERMAN ELWYN.

This paper will be published in full, with discussion, in a later issue of the ARCHIVES.

The Ocular Fundus in Urologic Disease Associated with Systemic Hypertension. DR. MARTIN COHEN.

This paper will be published in full, with discussion, in a later issue of the ARCHIVES.

Ocular Changes Associated with Experimental Renal Hypertension. DR. IRVING GRAEF and DR. ROBERT K. LAMBERT.

Experimental renal hypertension was induced in 35 dogs by the application of a Goldblatt clamp to the renal arteries or by a constricting envelope of cellophane or silk about the kidneys. The dogs were prepared by Dr. Irvine Page. The ocular effects were compared with those in cases of neurogenic hypertension, bilateral nephrectomy and nephrotoxic nephritis. Normal dogs were used as controls.

Acute malignant hypertension was manifest in 23 dogs as increased blood pressure (extreme in 11 dogs and inconstant in 9 dogs), retention of urea nitrogen (20 dogs) and acute necrotizing arteriolitis in the viscera (all dogs). These animals were examined five to sixty-five days after preparation. Clinically, hemorrhage and retinal detachment were constant ocular lesions. The arterial lesions affected the uveal tract, both the anterior and the posterior portion. Edema and arteriolitis of the choroid were common, but not constant. The retinal "arterioles" were not altered to the same degree as were the choroidal vessels of similar size, although some capillary hemorrhages and disorganization of pigment were observed. The arterioles of the optic nerve were rarely affected, and arterioles external to the globe were never involved.

Eight other dogs which died of malignant hypertension from three months to one year after the onset of hypertension showed similar necrotizing lesions. The blood pressure was higher and more sustained in these animals than in the dogs with more acute malignant hypertension, and the retention of urea nitrogen was pronounced in all the animals. Arterial lesions in the viscera were again matched by those in the eyes. In addition, hypertrophy of the media of the small ocular arteries and arterioles was seen in 2 animals of this group and in other dogs examined from two to four years later.

Ocular lesions were not noted as a result of neurogenic hypertension or after bilateral nephrectomy.

On the basis of this study, significant vascular changes in the eyes accompanying experimental renal hypertension appear to be associated usually with severe impairment of renal function and mild or severe hypertension and regularly with distinctive necrotizing lesions affecting the visceral arteries and arterioles in dogs. While retention of urea is commonly associated with malignant

hypertension, it may be insignificant in some animals; hypertension, especially in cases of the rapidly fatal form, may vary from slight to severe, or the blood pressure may fall to normal before death. The lesions in the vessels appear to be of toxic origin and are coincidental as far as retention of urea or hypertension is concerned.

In animals with the benign phase of hypertension no degenerative or sclerotic vascular lesions were encountered. Hypertrophy of the media was seen on occasion in the arteries of the choroid and iris, after benign renal hypertension of one year's duration. The retinal arterioles remained unchanged in this phase. The high frequency of hemorrhagic and necrotizing lesions in the iris and the ciliary body and processes in dogs is probably due to the peculiar arterial supply of the anterior portion of the uveal tract.

CORRECTION

In the article by Dr. H. Saul Sugar entitled "Guides in the Operative (Cosmetic) Treatment of Nonaccommodative Concomitant Squint in Adults," in the November issue (ARCH. OPHTH. 30: 593, 1943), the following corrections should be made:

On page 599, line 4, "0.6 prism diopter" should read "8 prism diopters," and, line 5, "resection" should read "recession."

On page 601, the first sentence of the second paragraph under "Convergent Squint" should read "When the deviation for distance is greater than that for near vision, the deviation is of the divergence insufficiency type."

In the fifth line of the paragraph with the heading "Divergent Squint," "divergence insufficiency type" should read "convergence insufficiency type."

The fifth and the last paragraph on the same page, entitled "Convergence Insufficiency Type" and "Divergence Insufficiency Type," are correct as published, but the two paragraphs should be transposed.

Book Reviews

Corneal Transplantation with Fresh, Preserved and Fixed Material: Experimental and Clinical Observations. By O. I. Shershewskaya. Price, 12 rubles. Pp. 201, with 80 illustrations. Novosibirsk, U. S. S. R., Soviet Siberia Publishers, 1940.

In this monograph Shershewskaya, senior assistant at the state institute for postgraduate and clinical study in Novosibirsk, U. S. S. R., reports the results of her experimental and clinical work on the possibility of the take and retention of transparency of formaldehyde-fixed corneal disks 4 mm. in width. The book is a comprehensive and serious review of the subject and consists of eight chapters.

The first chapter gives a detailed history of keratoplasty, starting with Reisinger's first report, in 1824, von Hippel's work on total leukoma, Zirma's famous case, in 1907, and Elschnig's work in the clinic at Prague, which served as the basis of keratoplasty all over the world. Elschnig performed 203 corneal transplantations from 1908 to 1930, with resulting transparent union of the transplant in 20 per cent. Filatov and his associates performed 455 corneal transplantations from 1922 to 1938; in 264 of these operations preserved cornea from the cadaver was used, and successful results were obtained in about 67 per cent. Castroviejo, of the United States, published his results in 80 keratoplastic operations on the human eye. Such operations are performed at present in all leading ophthalmic hospitals of the Soviet Union.

In the second chapter are reviewed the present technic of keratoplasty, fixation of the transplant, complications of the operation, instruments used, partial penetration, total keratoplasty and alloplasty (with use of an artificial cornea of inorganic material). The author gives a complete description of the methods used, with drawings to illustrate the operation and the instruments used by Elschnig, Filatov, Thomas, Castroviejo, Kraupa, Löwenstein, Löhlein and others.

The material used in the operation, the indications for keratoplasty, the postoperative course and the complications are discussed in the third, fourth and fifth chapters. In the Soviet Union conditions in the donor which contraindicate the use of corneal transplants are syphilis, miliary tuberculosis, septicemia, malignant tumors and diabetes; the age, sex and blood type of the donor are not important. The most favorable results were obtained with corneas of cadavers, preserved in whole or in citrated blood at a temperature of + 3 C. The time of preservation may be as long as fifteen days, although not more than four or five days is considered the optimal period. The transplant is kept dry in a Petri dish with the epithelial surface up. Interstitial keratitis and leukoma following scrofula, i. e., nonadherent leukoma, with a deep anterior chamber, are most favorable for successful keratoplasty; normal intraocular tension, absence of inflammation of the eye and a good physical condition are essential for satisfactory results.

The most troublesome complications are the secondary opacification of the transplant, appearance of scar tissue behind the transplant and glaucoma. The various methods of combating these complications are reviewed. Filatov obtained good results in treating the opaque transplant by additional keratoplastic work about the transplant.

The sixth chapter is devoted to the histogenesis associated with keratoplasty. A review of the subject indicates that the cornea has the quality of regeneration and that it is transplantable. Histologic observations on the transplant by various authors are cited. Saltzer's brilliant experiments in transplantation of dead organic tissue, formaldehyde-fixed corneal disks, and the investigations of other authors on regeneration of the cornea indicate two directions which union of tissues may take: (1) true transplantation, with the change in the disk (Fuchs, Ascher, Elschnig,

Filatov) and (2) gradual substitution of the transplant by the regenerated tissue of the host, the transplant thus only stimulating the surrounding corneal tissue to regeneration (Saltzer, Ribbert, Thomas, Castroviejo).

Shershewskaya's own experimental results are described in chapter 7. In her study, undertaken to verify Saltzer's experiments, she used penetrating homoplastic corneas, and the size of the corneal disk was 4 mm., instead of the 2 mm. employed by Saltzer. The enucleated rabbit eye was kept for two days in a 4 per cent concentration of solution of formaldehyde U.S.P. and then for four days in isotonic solution of three chlorides U.S.P. Thirty operations were done on 37 rabbits, all with transparent corneas; in only 2 was there leukoma after a thermic burn. Union took place in 12 rabbits; of these, transplants were transparent in 3, semitransparent in 1 and opaque in 8. The time of observation was from nine to fourteen months. The low rate of "takes" was due partly to overcrowded conditions in the animal house, as the rabbits operated on were not isolated. The take of the formaldehyde-fixed transplants confirms Saltzer's observation that after a certain time the transplant is reabsorbed and replaced by the young, regenerated fibers of the host. The results of histopathologic study, records of the operation and photographs of the eyes illustrate the experiments.

The eighth, and last, chapter is devoted to clinical observations. The author performed 35 keratoplastic operations on 32 patients; in 21 of these procedures the prognosis was unfavorable (total or partial leukoma, faulty light projections or high intraocular tension), and the operation was done because of the pressing desire of the patient. Of the 11 operations with favorable prognosis, there were 6 transparent and 4 semitransparent takes and 1 opaque one. The technic of the operation, with the author's modifications, drawings, a number of tables and detailed histories are presented.

Shershewskaya performed 5 transplantations with formaldehyde-fixed corneal disks; since it was the first attempt to perform the operation on the human eye (except in Ascher's case, in which it was unsuccessful), she used 3 patients with the most hopeless outlook and 2 with fair indications for keratoplasty. She obtained 1 opaque, 2 semitransparent and 1 transparent take, and in the fifth the transplant was lost. Thus her work with formaldehyde-treated disks on animal and human eyes proved that it was possible to obtain a take. The use of formaldehyde-treated corneal disks would solve the problem of the donor. Histologic examination of the transplants in rabbits showed no definite border, as the stroma of the host blended with the fibers of the transplant. The postoperative course with the fixed disks is similar to that of unfixed transplants.

OLGA SITCHEVSKA.

Biomicroscopy of the Eye: Slit Lamp Microscopy of the Living Eye. Volume 1. By M. L. Berliner, M.D., Assistant Professor of Clinical Surgery (Ophthalmology), Cornell University Medical College; Assistant Surgeon, New York Eye and Ear Infirmary. Price, $17.50. Pp. 709, with 512 illustrations, including 40 pages of color plates. New York: Paul B. Hoeber, Inc., 1943.

"Biomicroscopy of the Eye," written to supply instruction in the technic of biomicroscopy, fills a definite need, as there is no adequate book in English on this important subject. It not only describes the required apparatus and how to use it but gives a complete and illustrated description of the findings under normal and pathologic conditions.

Volume 1 deals with the conjunctiva, eyelids, cornea and anterior chamber; volume 2, which is to follow, will discuss the iris, vitreous and lens. After a short historical sketch, the various types of biomicroscopes are described, and their manipulation is explained. The technic, according to the author, is not as difficult as it is claimed to be. The various steps are clearly stated, and the student will obtain as much information on the use of the slit lamp as can be given in a written description. Due emphasis is placed on exact localization, which Vogt particularly stressed and which formerly was only partially possible with the means

at hand. Methods of determination of the depth of the anterior chamber are given. The excellent chapter on technic concludes with a brief summary of the best order of procedure for efficient examination of the eye with the biomicroscope. The next chapters consist of a systematic survey of the conjunctiva, the margin of the eyelids and sclera, the cornea and the anterior chamber. After review of the normal histology, the normal, noninflammatory and inflammatory conditions and tumor formations are described, with valuable references to the clinical appearance and course of disease processes. The chapter on the anterior chamber deserves mention; in it are described Kronfeld's investigations, Roenne's colloidometer, thermal convection currents and changes in the aqueous. This leads naturally to the examination of the angle of the anterior chamber, "gonioscopy," which is written by Dr. H. Saul Sugar. The development of a suitable contact glass, the focal illuminating system, a suitable microscope and the technic are fully described. Presentation of this examination, which is so important, particularly in cases of glaucoma, is admirable and confirms the belief that gonioscopy should advance knowledge of the complications that follow operations for cataract and glaucoma.

Illustrations form an all-important part of a treatise of this kind. There are 512 illustrations, including 40 pages of color plates. They are excellently selected, and the beauty of the colored drawings reflects great credit on the artist, as well as on the publisher for their successful reproduction. The author has written a scientific, comprehensive and valuable book, which will be of great assistance to every student of ophthalmology, both to the beginner and to the active practitioner.

ARNOLD KNAPP.

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All correspondence should be addressed to the secretary, Dr. Mohammed Khalil.

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Secretary-Treasurer: Dr. F. A. Anderson, 12 St. John's Hill, Shrewsbury, England.
Place: Oxford, England. Time: July 8-9, 1943.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date.

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Secretary-Treasurer: Dr. W. H. Turnley, 1 Atlantic St., Stamford, Conn.

EYE, EAR, NOSE AND THROAT CLUB OF GEORGIA

President: Dr. E. N. Maner, 247 Bull St., Savannah.
Secretary-Treasurer:: Dr. C. K. McLaughlin, 567 Walnut St., Macon.

INDIANA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. F. McK. Ruby, Union City.
Secretary: Dr. Edwin W. Dyar Jr., 23 E. Ohio St., Indianapolis.
Place: French Lick. Time: First Wednesday in April.

IOWA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. J. K. Von Lackum, 117–3d St. S. E., Cedar Rapids.
Secretary-Treasurer: Dr. B. M. Merkel, 604 Locust St., Des Moines.

LOUISIANA-MISSISSIPPI OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President: Dr. Val H. Fuchs, 200 Carondelet St., New Orleans.
Secretary-Treasurer: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.

MICHIGAN STATE MEDICAL SOCIETY, SECTION OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman: Dr. Robert H. Fraser, 25 W. Michigan Ave., Battle Creek.
Secretary: Dr. R. G. Laird, 114 Fulton St., Grand Rapids.

MINNESOTA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. George E. McGeary, 920 Medical Arts Bldg., Minneapolis.
Secretary: Dr. William A. Kennedy, 372 St. Peter St., St. Paul.
Time: Second Friday of each month from October to May.

MONTANA ACADEMY OF OTO-OPHTHALMOLOGY

President: Dr. William Morrison, 208 N. Broadway, Billings, Mont.
Secretary: Dr. Fritz D. Hurd, 309 Medical Arts Bldg., Great Falls.

NEBRASKA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John Peterson, 1307 N St., Lincoln.

NEW JERSEY STATE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY, OTOLOGY AND RHINOLARYNGOLOGY

Chairman: Dr B. E. Failing, 31 Lincoln Park, Newark.
Secretary: Dr. George Meyer, 410 Haddon Ave., Camden.

NEW YORK STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

Chairman: Dr. Searle B. Marlow, 109 S. Warren St., Syracuse.
Secretary: Dr. C. Stewart Nash, 277 Alexander St., Rochester.

NORTH CAROLINA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Hugh C. Wolfe, 102 N. Elm St., Greensboro.
Secretary: Dr. Vanderbilt F. Couch, 104 W. 4th St., Winston-Salem.

NORTH DAKOTA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. T. W. Buckingham, 405 Broadway, Bismarck.
Secretary-Treasurer: Dr. F. L. Wicks, 516–6th St., Valley City.

OREGON ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Paul Neely, 1020 S. W. Taylor St., Portland.
Secretary-Treasurer: Dr. Lewis Jordon, 1020 S. W. Taylor St., Portland.
Place: Good Samaritan Hospital, Portland. Time: Third Tuesday of each month.

RHODE ISLAND OPHTHALMOLOGICAL AND OTOLOGICAL SOCIETY

Acting President: Dr. N. Darrell Harvey, 112 Waterman St., Providence.
Secretary-Treasurer: Dr. Linley C. Happ, 124 Waterman St., Providence.
Place: Rhode Island Medical Society Library, Providence. Time: 8:30 p. m., second Thursday in October, December, February and April.

SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. J. L. Sanders, 222 N. Main St., Greenville.
Secretary: Dr. J. H. Stokes, 125 W. Cheves St., Florence.

TENNESSEE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Wesley Wilkerson, 700 Church St., Nashville.
Secretary-Treasurer: Dr. W. D. Stinson, 124 Physicians and Surgeons Bldg., Memphis.

TEXAS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. F. H. Rosebrough, 603 Navarro St., San Antonio.
Secretary: Dr. M. K. McCullough, 1717 Pacific Ave., Dallas.

UTAH OPHTHALMOLOGICAL SOCIETY

President: Dr. Everett B. Muir, Boston Bldg., Salt Lake City.
Secretary-Treasurer: Dr. Earl H. Phillips, 623 Judge Bldg., Salt Lake City.
Place: University Club, Salt Lake City. Time: 7:00 p. m., third Monday of each month.

VIRGINIA SOCIETY OF OTO-LARYNGOLOGY AND OPHTHALMOLOGY

President: Dr. Mortimer H. Williams, 30½ Franklin Rd. S. W., Roanoke.
Secretary-Treasurer: Dr. Meade Edmunds, 34 Franklin St., Petersburg.

WEST VIRGINIA STATE MEDICAL ASSOCIATION, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. George Traugh, 309 Cleveland Ave., Fairmont.
Secretary: Dr. Welch England, 621½ Market St., Parkersburg.

LOCAL

AKRON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. E. L. Mather, 39 S. Main St., Akron, Ohio.
Secretary-Treasurer: Dr. V. C. Malloy, 2d National Bank Bldg., Akron, Ohio.
Time: First Monday in January, March, May and November.

ATLANTA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. B. M. Cline, 153 Peachtree St. N. E., Atlanta, Ga.
Acting Secretary: Dr. A. V. Hallum, 478 Peachtree St. N. E., Atlanta, Ga.
Place: Grady Hospital. Time: 6:00 p. m., fourth Monday of each month, from October to May.

BALTIMORE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY

Chairman: Dr. Ernst Bodenheimer, 1212 Eutaw Pl., Baltimore.
Secretary: Dr. Thomas R. O'Rourk, 104 W. Madison St., Baltimore.
Place: Medical and Chirurgical Faculty, 1211 Cathedral St. Time: 8:30 p. m., fourth Thursday of each month from October to March.

BIRMINGHAM EYE, EAR, NOSE AND THROAT CLUB

President: Each member, in alphabetical order.
Secretary: Dr. Luther E. Wilson, 919 Woodward Bldg., Birmingham, Ala.
Place: Tutwiler Hotel. Time: 6:30 p. m., second Tuesday of each month, September to May, inclusive.

Brooklyn Ophthalmological Society

President: Dr. William B. Agan, 1 Nevins St., Brooklyn.
Secretary-Treasurer: Dr. Benjamin C. Rosenthal, 140 New York Ave., Brooklyn.
Place: Kings County Medical Society Bldg., 1313 Bedford Ave. Time: Third Thursday in February, April, May, October and December.

Buffalo Ophthalmologic Club

President: Dr. Walter F. King, 519 Delaware Ave., Buffalo.
Secretary-Treasurer: Dr. Sheldon B. Freeman, 196 Linwood Ave., Buffalo.
Time: Second Thursday of each month.

Chattanooga Society of Ophthalmology and Otolaryngology

President: Each member, in alphabetical order.
Secretary: Dr. Douglas Chamberlain, Chattanooga Bank Bldg., Chattanooga, Tenn.
Place: Mountain City Club. Time: Second Thursday of each month from September to May.

Chicago Ophthalmological Society

President: Dr. Vernon M. Leech, 55 E. Washington St., Chicago.
Secretary: Dr. W. A. Mann, 30 N. Michigan Ave., Chicago.
Place: Chicago Towers Club, 505 N. Michigan Ave. Time: Third Monday of each month from October to May.

Cincinnati General Hospital Ophthalmology Staff

Chairman: Dr. D. T. Vail, 441 Vine St., Cincinnati.
Secretary: Dr. A. A. Levin, 441 Vine St., Cincinnati.
Place: Cincinnati General Hospital. Time: 7:45 p. m., third Friday of each month except June, July and August.

Cleveland Ophthalmological Club

Chairman: Dr. Shandor Monson, 1621 Euclid Ave., Cleveland.
Secretary: Dr. Carl Ellenberger, 14805 Detroit Ave., Cleveland.
Time: Second Tuesday in October, December, February and April.

College of Physicians, Philadelphia, Section on Ophthalmology

Chairman: Dr. Alfred Cowan, 1930 Chestnut St., Philadelphia.
Clerk: Dr. W. S. Reese, 1901 Walnut St., Philadelphia.
Time: Third Thursday of every month from October to April, inclusive.

Columbus Ophthalmological and Oto-Laryngological Society

Chairman: Dr. H. D. Emswiler, 370 E. Town St., Columbus, Ohio.
Secretary-Treasurer: Dr. D. G. Sanor, 206 E. State St., Columbus, Ohio.
Place: The Neil House. Time: 6 p. m., first Monday of each month.

Corpus Christi Eye, Ear, Nose and Throat Society

Chairman: Dr. Arthur Padillo, 414 Medical Professional Bldg., Corpus Christi, Texas.
Secretary: Dr. Edgar G. Mathis, 815 Medical Arts Bldg., Corpus Christi, Texas.
Time: Second Friday of each month from October to May.

Dallas Academy of Ophthalmology and Oto-Laryngology

President: Dr. S. F. Harrington, 921 Medical Arts Bldg., Dallas, Texas.
Secretary: Dr. Abell Hardin, Medical Arts Bldg., Dallas, Texas.
Place: Dallas Athletic Club. Time: 6:30 p. m., first Tuesday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Des Moines Academy of Ophthalmology and Otolaryngology

President: Dr. H. C. Schmitz, 604 Locust St., Des Moines, Iowa.
Secretary-Treasurer: Dr. Byron M. Merkel, 604 Locust St., Des Moines, Iowa.
Time: 7:45 p. m., third Monday of every month from September to May.

Detroit Ophthalmological Club

Chairman: Dr. Howell L. Begle, 2730 E. Jefferson Ave., Detroit.
Secretary: Dr. C. W. Lepard, 1025 David Whitney Bldg., Detroit.
Time: 6:30 p. m., first Wednesday of each month, November through April.

Detroit Ophthalmological Society

President: Dr. Parker Heath, 1553 Woodward Ave., Detroit.
Secretary: Dr. Leland F. Carter, 1553 Woodward Ave., Detroit.
Place: Club rooms of Wayne County Medical Society. Time: Third Thursday of each month from November to April, inclusive.

Eastern New York Eye, Ear, Nose and Throat Association

President: Appointed at each meeting.
Secretary-Treasurer: Dr. Joseph L. Holohan, 330 State St., Albany.
Time: Third Wednesday in October, November, March, April, May and June.

Eastern Pennsylvania Association of Eye, Ear, Nose and Throat Physicians

President: Dr. James E. Landis, 232 N. 6th St., Reading.
Secretary-Treasurer pro tem: Dr. Paul C. Craig, 232 N. 5th St., Reading.
Time: Last week in April each year.

Fort Worth Eye, Ear, Nose and Throat Society

President: Dr. Rex Howard, 602 W. 10th St., Fort Worth, Texas.
Secretary-Treasurer: Dr. R. H. Gough, Medical Arts Bldg., Fort Worth, Texas.
Place: Medical Hall, Medical Arts Bldg. Time: 7:30 p. m., first Friday of each month except July and August.

Houston Academy of Medicine, Ophthalmological and Oto-Laryngological Section

President: Dr. Felician J. Slataper, 1110-1111 Medical Arts Bldg., Houston, Texas.

Secretary: Dr. Theo. L. Holland, 611 Medical Arts Bldg., Houston, Texas.

Place: Medical Arts Bldg., Harris County Medical Society Rooms. Time: 8 p. m., second Thursday of each month from September to June.

Indianapolis Ophthalmological and Oto-laryngological Society

President: Dr. Myron Harding, 23 E. Ohio St., Indianapolis.

Secretary: Dr. Kenneth L. Craft, 23 E. Ohio St., Indianapolis.

Place: Indianapolis Athletic Club. Time: 6:30 p. m., second Thursday of each month from November to May.

Kansas City Society of Ophthalmology and Oto-Laryngology

President: Dr. Edgar Johnson, 906 Grand Ave., Kansas City, Mo.

Secretary: Dr. W. E. Keith, 1103 Grand Ave., Kansas City, Mo.

Time: Third Thursday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Long Beach Eye, Ear, Nose and Throat Society

Chairman: Dr. Harold Snow, 614 S. Pacific Ave., San Pedro, Calif.

Secretary-Treasurer: Dr. Oliver R. Nees, 508 Times Bldg., Long Beach, Calif.

Place: Professional Bldg. Time: Last Wednesday of each month from October to May.

Los Angeles Society of Ophthalmology and Otolaryngology

President: Dr. Sylvester H. Welch, 102 N. Brand Blvd., Glendale, Calif.

Secretary-Treasurer: Dr. Orrie E. Ghrist, 210 N. Central Ave., Glendale, Calif.

Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: 6:00 p. m., fourth Monday of each month from September to May, inclusive.

Louisville Eye and Ear Society

President: Dr. Joseph S. Heitger, Heyburn Bldg., Louisville, Ky.

Secretary-Treasurer: Dr. J. W. Fish, 321 W. Broadway, Louisville, Ky.

Place: Brown Hotel. Time. 6:30 p. m., second Thursday of each month from September to May, inclusive.

Lower Anthracite Eye, Ear, Nose and Throat Society

Chairman: Each member in alphabetical order.

Secretary: Dr. James J. Monohan, 31 S. Jardin St., Shenandoah, Pa.

Medical Society of the District of Columbia, Section of Ophthalmology and Otolaryngology

Chairman: Dr. P. S. Constantinople, 1835 I St. N. W., Washington.

Secretary: Dr. Frazier Williams, 1801 I St. N. W., Washington.

Place: 1718 M St. N. W. Time: 8 p. m., third Friday of each month from October to April, inclusive.

Memphis Society of Ophthalmology and Otolaryngology

Chairman: Each member in alphabetical order.

Secretary: Dr. Sam H. Sanders, 1089 Madison Ave., Memphis, Tenn.

Place: Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital. Time: 8 p. m., second Tuesday of each month from September to May.

Milwaukee Oto-Ophthalmic Society

President: Dr. Edwin C. Bach, 324 E. Wisconsin Ave., Milwaukee.

Secretary-Treasurer: Dr. Ralph T. Rank, 238 W. Wisconsin Ave., Milwaukee.

Place: University Club. Time: 6:30 p. m., second Tuesday of each month.

Montgomery County Medical Society

Chairman: Dr. H. V. Dutrow, 1040 Fidelity Medical Bldg., Dayton, Ohio.

Secretary-Treasurer: Dr. Maitland D. Place, 981 Reibold Bldg., Dayton, Ohio.

Place: Van Cleve Hotel. Time: 6:30 p. m., first Tuesday of each month from October to June, inclusive.

Montreal Ophthalmological Society

President: Dr. J. Rosenbaum, 1396 Ste. Catherine St. W., Montreal, Canada.

Secretary: Dr. L. Tessier, 1230 St. Joseph Blvd. E., Montreal, Canada.

Time: Second Thursday of October, December, February and April.

Nashville Academy of Ophthalmology and Otolaryngology

Chairman: Dr. M. M. Cullom, 700 Church St., Nashville, Tenn.

Secretary: Dr. R. E. Sullivan, 432 Doctors Bldg., Nashvile, Tenn.

Place: St. Thomas Hospital. Time: 8 p. m., third Monday of each month from October to May.

New Haven Ophthalmological Society

President: Dr. William H. Ryder, 185 Church St., New Haven, Conn.

Secretary: Dr. Frederick A. Wiess, 255 Bradley St., New Haven, Conn.

New Orleans Ophthalmological and Oto-laryngological Society

President: Dr. W. B. Clark, 1012 American Bank Bldg., New Orleans.

Secretary: Dr. Mercer G. Lynch, 1018 Maison Blanche Bldg., New Orleans.

Place: Louisiana State University Medical Bldg. Time: 8 p. m., second Tuesday of each month from October to May.

New York Academy of Medicine, Section of Ophthalmology

Chairman: Dr. Frank C. Keil, 660 Madison Ave., New York.
Secretary: Dr. Willis S. Knighton, 121 E. 61st St., New York.
Time: 8:30 p. m., third Monday of every month from October to May, inclusive.

New York Society for Clinical Ophthalmology

President: Dr. Sigmund Agatston, 875–5th Ave., New York.
Secretary: Dr. Benjamin Esterman, 983 Park Ave., New York.
Place: Squibb Hall, 745–5th Ave. Time: 8 p. m., first Monday of each month from October to May, inclusive.

Oklahoma City Academy of Ophthalmology and Otolaryngology

President: Dr. James P. Luton, 117 N. Broadway, Oklahoma City.
Secretary: Dr. Harvey O. Randel, 117 N. Broadway, Oklahoma City.
Place: University Hospital. Time: Second Tuesday of each month from September to May.

Omaha and Council Bluffs Ophthalmological and Oto-Laryngological Society

President: Dr. D. D. Stonecypher, Nebraska City, Neb.
Secretary-Treasurer: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Place: Omaha Club, 20th and Douglas Sts., Omaha. Time: 6 p. m. dinner; 7 p. m. program; third Wednesday of each month from October to May.

Passaic-Bergen Ophthalmological Club

President: Dr. Thomas Sanfacon, 340 Park Ave., Paterson, N. J.
Secretary-Treasurer: Dr. J. Averbach, 435 Clinton Ave., Clinton, N. J.
Place: Paterson Eye and Ear Infirmary. Time: 9 p. m., last Friday of every month, except June, July and August.

Philadelphia County Medical Society, Eye Section

President: Dr. Wilfred E. Fry, 1819 Chestnut St., Philadelphia.
Secretary: Dr. Glen Gregory Gibson, 255 S. 17th St., Philadelphia.
Time: First Thursday of each month from October to May.

Pittsburgh Ophthalmological Society

President: Dr. John B. McMurray, 6 S. Main St., Washington, Pa.
Secretary: Dr. George H. Shuman, 351–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine Bldg. Time: Fourth Monday of each month, except June, July, August and September.

Reading Eye, Ear, Nose and Throat Society

President: Dr. R. M. Brickbauer, Shillington, Pa.
Secretary: Dr. Paul C. Craig, 232 N. 5th St., Reading, Pa.
Place: Wyomissing Club. Time: 6:30 p. m., third Wednesday of each month from October to July.

Richmond Ophthalmological and Oto-Laryngological Society

President: Dr. Peter N. Pastore, Medical College of Virginia, Richmond, Va.
Secretary: Dr. Clifford A. Folkes, Professional Bldg., Richmond, Va.
Place: Westmoreland Club. Time: 6 p. m., second Monday of each month from October to May.

Rochester Eye, Ear, Nose and Throat Society

President: Dr. Frank Barber, 75 S. Fitzhugh St., Rochester, N. Y.
Secretary-Treasurer: Dr. Charles T. Sullivan, 277 Alexander St., Rochester, N. Y.

St. Louis Ophthalmic Society

President: Dr. C. C. Beisbarth, 3720 Washington Blvd., St. Louis.
Secretary: Dr. H. R. Hildreth, 508 N. Grand Blvd., St. Louis.
Place: Oscar Johnson Institute. Time: Clinical meeting, 5:30 p. m., dinner and scientific meeting 6:30 p. m., fourth Friday of each month from October to April, inclusive, except December.

San Antonio Ophthalmo-Oto-Laryngological Society

President: Dr. Belvin Pritchett, 705 E. Houston St., San Antonio 5, Texas.
Secretary-Treasurer: Lt. Col. John L. Matthews, AAF School of Aviation Medicine, Randolph Field, Texas.
Place: San Antonio, Brooke General Hospital, Randolph Field or San Antonio Aviation Cadet Center. Time: 7 p. m., second Tuesday of each month from October to May.

San Francisco County Medical Society, Section on Eye, Ear, Nose and Throat

Chairman: Dr. Roy H. Parkinson, 870 Market St., San Francisco.
Secretary: Dr. A. G. Rawlins, 384 Post St., San Francisco.
Place: Society's Bldg., 2180 Washington St., San Francisco. Time: Fourth Tuesday of every month except June, July and December.

Shreveport Eye, Ear, Nose and Throat Society

President: Dr. David C. Swearingen, Slattery Bldg., Shreveport, La.
Secretary-Treasurer: Dr. Kenneth Jones, Medical Arts Bldg., Shreveport, La.
Place: Shreveport Charity Hospital. Time: 7:30 p. m., first Monday of every month except July, August and September.

Spokane Academy of Ophthalmology and Oto-Laryngology

President: Dr. Clarence A. Veasey Sr., 421 W. Riverside Ave., Spokane, Wash.
Secretary: Dr. Clarence A. Veasey Jr., 421 W. Riverside Ave., Spokane, Wash.
Place: Paulsen Medical and Dental Library. Time: 8 p. m., fourth Tuesday of each month except June, July and August.

Syracuse Eye, Ear, Nose and Throat Society

President: Dr. A. H. Rubenstein, 713 E. Genesee St., Syracuse, N. Y.
Secretary-Treasurer: Dr. I. H. Blaisdell, 713 E. Genesee St., Syracuse, N. Y.
Place: University Club. Time: First Tuesday of each month except June, July and August.

Toledo Eye, Ear, Nose and Throat Society

Chairman: Dr. E. A. Orwig, 420 Madison Ave., Toledo, Ohio.
Secretary: Dr. E. W. Campbell, 316 Michigan St., Toledo, Ohio.
Place: Toledo Club. Time: Each month except June, July and August.

Toronto Academy of Medicine, Section of Ophthalmology

Chairman: Dr. W. R. F. Luke, 316 Medical Arts Bldg., Toronto, Canada.
Secretary: Dr. W. T. Gratton, 216 Medical Arts Bldg., Toronto, Canada.
Place: Academy of Medicine, 13 Queens Park. Time: First Monday of each month, November to April.

Washington, D. C., Ophthalmological Society

President: Dr. S. Bockoven, 1752 Massachusetts Ave., Washington, D. C.
Secretary-Treasurer: Dr. John Lloyd, 1218–16th St. N. W., Washington, D. C.
Place: Medical Society of District of Columbia Bldg., 1718 M St. N. W., Washington, D. C. Time: 7:30 p. m., first Monday in November, January, March and May.

Wilkes-Barre Ophthalmological Society

Chairman: Each member in turn.
Secretary: Dr. Samuel T. Buckman, 70 S. Franklin St., Wilkes-Barre, Pa.
Place: Office of chairman. Time: Last Tuesday of each month from October to May.